

CHAPTER 8

Acid–base homeostasis and derangements

Jon Palmer

Director of Perinatology/Neonatology Programs, Chief, Neonatal Intensive Care Service, Graham French Neonatal Section, Connelly Intensive Care Unit, New Bolton Center, University of Pennsylvania, USA

Acid–base abnormalities are common in horses requiring fluid therapy. Carefully characterizing the acid–base abnormality can point to the underlying disruption of the horse’s physiology and give important clues to the underlying disease process that is responsible for the need for fluid therapy. There are multiple clinical approaches used to evaluate acid–base abnormalities. Which technique is used is more a matter of style than being correct or incorrect. The goal of all of these approaches is an understanding of the components of the acid–base abnormality, which will aid in formulating a rational approach to therapy.

Physiology of acid–base balance

Regulation of acid–base homeostasis

Blood pH is very tightly regulated. Hydrogen ion concentration $[H^+]$ is extremely low, averaging 0.00004 mEq/L (Collings, 2010). In contrast, the interstitial fluid concentration of sodium is 3.5 million times higher than this value. The normal variation in H^+ concentration in extracellular fluid is only about one millionth as great as the normal variation in sodium ion concentration. This precision in H^+ regulation is vital because of the effect of pH on protein configurations, enzyme activity, transcellular ion transport mechanisms, and other vital cellular functions. It is also important in drug distribution, binding, and activity. Thus tight H^+ concentration regulation is very important in maintaining the health of the patient and the effectiveness of therapeutic interventions.

The mechanisms in place to maintain H^+ homeostasis are well coordinated. The acid–base balance is controlled by the lungs, kidneys, and a buffer system distributed between the blood, interstitial fluid, cells, and bone. All of these systems interact and respond to physiologic changes. The first line of defense responding to acid–base changes is the buffering system. This buffering system is composed of a variety of weak acids that are also components of the most basic cellular physiology. These buffers, by virtue of being within and surrounding the cells, protect the cellular metabolism from the negative effects of acid–base disturbances. The most important participants in this buffering system include the bicarbonate/carbonic acid buffer, intracellular and extracellular proteins (such as albumin, globulins, and hemoglobin), inorganic ions (such as phosphate and sulfate), and bone (which contains a large reservoir of bicarbonate and phosphate, which can actively buffer a significant acute acid load) (Collings, 2010).

Acid is a major by-product of normal metabolism that needs to be buffered and excreted efficiently, in order to avoid acidosis. Oxidation of carbon-containing fuels produces carbon dioxide (CO_2), resulting in the generation of 15,000 to 20,000 mEq of H^+ daily, which is excreted by respiration (DuBose, 2012; Kellum, 2005). In contrast, only 0.3–1 mEq/kg of anions are excreted through the kidney each day (DuBose, 2012). Hemoglobin is the major buffer of volatile acid. Deoxyhemoglobin is an active base. Within the erythrocyte CO_2 combines with H_2O , under the influence of carbonic anhydrase, to form H_2CO_3 . This ionizes to hydrogen and bicarbonate. Hydrogen ions bind to

histidine residues on deoxyhemoglobin (the “Haldane” effect), and bicarbonate is actively pumped from cells. Chloride moves inward to maintain electroneutrality (chloride shift) and to ensure the continued production of carbonic acid.

Carbon dioxide is also buffered directly by combining with hemoglobin (carbaminohemoglobin) and plasma proteins (carbamino proteins). The CO_2 added to venous blood is usually distributed as follows: 65% as HCO_3^- and H^+ bound to hemoglobin, 27% as carbaminohemoglobin (CO_2 bound to hemoglobin), and 8% dissolved. When respiratory failure occurs, the principal CO_2 buffering system, hemoglobin, becomes overwhelmed. This leads to the rapid development of acidosis. Severe anemia may decrease this buffering capacity (DuBose, 2011; Kellum, 2005).

Under resting conditions, Pco_2 is maintained within a narrow range by a negative feedback regulator involving two sets of chemoreceptors that sense $[\text{H}^+]$, one in the brain (central chemoreceptors) and one in the carotid bodies (peripheral chemoreceptors). When these chemoreceptors sense an increase in $[\text{H}^+]$, breathing is stimulated. This chemoreflex control system also protects against asphyxia by increasing the sensitivity of the peripheral chemoreceptors to $[\text{H}^+]$ under conditions of hypoxia. CO_2 concentration can be adjusted rapidly and precisely by the respiratory center in defense of arterial and body pH. Conversely, alterations in Pco_2 due to changes in alveolar ventilation can be the primary cause of abnormalities in pH.

In addition to the production of CO_2 , metabolism generates a daily load of other acids (lactate, citrate, acetate, and pyruvate), which must be removed by other metabolic reactions. In general these are products that are further metabolized to CO_2 . Organic acids are derived from intermediary metabolites formed by partial combustion of dietary carbohydrates, fats, and proteins as well as from nucleic acids (uric acid). The organic acid generated contributes to net endogenous acid production when the conjugate bases are excreted in the urine as organic anions. If full oxidation of these acids can occur, however, H^+ is reclaimed and eliminated as CO_2 and water. The complete combustion of carbon involves the intermediate generation and metabolism of 2000 to 3000 mmol of relatively strong organic acids, such as lactic acid, tricarboxylic acids, ketoacids, or other acids, depending on the type of fuel consumed. These organic acids do not accumulate in the body under most

circumstances, with concentrations remaining in the low millimolar range. If production and consumption rates become mismatched, however, these organic acids can accumulate causing significant metabolic acidosis (e.g., lactic acid accumulation in septic shock or with muscle activity) (DuBose, 2012).

Although temporary relief from changes in the pH of extracellular fluid may be derived from buffering or respiratory compensation, the ultimate defense against addition of non-volatile acid or of alkali resides in the kidneys. The metabolism of some body constituents such as proteins, nucleic acids, and small fractions of lipids and certain carbohydrates generates specific organic acids that cannot be burned to CO_2 (e.g., uric, oxalic, glucuronic, hippuric acids). In addition, the inorganic acids H_2SO_4 (derived from oxidation of methionine and cysteine) and H_3PO_4 (derived from organophosphates), must be excreted by the kidneys or the gastrointestinal tract (DuBose, 2012). The major effect of the kidney on acid–base balance relates to the ability to excrete non-volatile acids and bases, and maintain and modify strong ion concentrations. Because dietary intake of sodium and chloride is roughly equal, the kidney excretes a net Cl^- load with NH_4^+ , a weak cation, to balance the charge in the urine. The control of excretion of Cl^- and NH_4^+ is the essence of metabolic (renal) compensation for acid–base abnormalities.

Each of these three acid–base-regulating systems dynamically responds to small changes in acid–base balance allowing for the precise physiologic control that is required for normal cellular function. Consequently, disorders of kidneys, lungs, and physiologic buffers can result in acid–base abnormalities. Physiologic insults such as gastric reflux, diarrhea, respiratory failure, kidney dysfunction, toxic ingestions, among others can result in life-threatening acid–base crises.

Consequences of acid–base abnormalities

Although acid–base abnormalities are an important sign of underlying disease, except in the most severe cases they are usually clinically silent being overshadowed by the signs produced by the primary problem. Patients with mild metabolic acidosis are often subclinical and the compensatory hyperventilation is usually not clinically evident. Initial respiratory compensation usually takes the form of less frequent but deeper breaths increasing alveolar ventilation by effectively decreasing dead space minute ventilation. This change often

escapes detection on clinical examination. Metabolic alkalosis is frequently overlooked until it is evident on laboratory evaluation. If hypoventilation resulting in respiratory acidosis is caused by neuromuscular or mechanical problems, the patient will be dyspneic and tachypneic. But if the respiratory center is impaired, as commonly occurs in neonatal encephalopathy, ventilation may be reduced without any sense of dyspnea.

When symptomatic or clinical, only the most extreme derangements of acid–base balance are fatal. Alterations in the relative concentrations of hydrogen ions are generally less important than the pathologic abnormalities causing them. The primary underlying disease process resulting in the acid–base abnormality is usually the direct cause of mortality in the patient before the acid–base derangement becomes extreme enough to be fatal. However, when extreme acid–base derangements occur or changes in the acid–base balance develop quickly, dangerous disruption to the normal physiologic responses may occur leading to organ dysfunction. When the acid–base abnormality is superimposed on the primary pathologic process, it can significantly contribute to serious morbidity and mortality. The type of acidosis is also important. Mortality is highest when lactate accumulation is the cause of acidosis (Gunnerson et al., 2006; Kellum, 2005).

Less extreme derangements can sometimes produce harm because of the patient's response to the abnormality. For example, a patient with metabolic acidosis will attempt to compensate by increasing minute ventilation. The workload that is imposed by increasing minute ventilation can lead to respiratory muscle fatigue with respiratory failure or diversion of blood flow from vital organs to the respiratory muscles resulting in organ injury. Acidemia will cause increased adrenergic tone, which can, in turn, promote the development of cardiac dysrhythmias and increase myocardial oxygen demand especially in patients that already have significant ischemia (Effros & Swenson, 2010; Greenbaum, 2011; Kellum, 2005; Shannon, 2007,).

Acidemia, especially when caused by metabolic acidosis, may have direct cardiovascular consequences. Initially acidosis will result in a positive inotropic effect secondary to the adrenergic response. However, as the pH falls to less than 7.2 there can be a negative inotropic effect caused by impaired myocardial contractility. Initially the heart rate increases but as the pH declines to less than 7.1, the heart rate may fall as well. With

acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in cases with volume depletion or shock. It also decreases the effectiveness of exogenous therapeutic adrenergic drugs when treating shock. Acidemia will also predispose to ventricular arrhythmias especially in the presence of high endogenous adrenergic tone or exogenous adrenergic drug therapy.

Arterial vasodilation and venoconstriction may also occur in the acidemic patient. Pulmonary hypertension may develop as a result of acidemia, which in the neonate can lead to retention of or reversion to fetal circulation. The negative inotropic effects of acidemia, along with fluid shifts to central circulation caused by the venoconstriction, may lead to pulmonary edema. These cardiovascular effects of acidosis can lead to a vicious cycle of decreased myocardial contractility that produces hypoperfusion, which in turn increases lactic acidosis, further impairing myocardial contractility and adrenergic responsiveness leading to refractory shock (Effros & Swenson, 2010; Greenbaum, 2011; Shannon, 2007).

The acid–base balance has direct effects on gas exchange. Patients with a respiratory acidosis breathing room air will always have hypoxemia (Effros & Swenson, 2010; Ijland et al., 2010). As predicted by the Bohr effect, acidemia produces a rightward shift of the oxyhemoglobin dissociation curve, decreasing the affinity for oxygen. This results in less efficient oxygen loading of hemoglobin in the lungs but enhanced unloading in the tissues. Alkalosis shifts the oxyhemoglobin dissociation curve to the left resulting in reduced oxygen delivery to tissues (Effros & Swenson, 2010; Ijland et al., 2010; Shannon 2007).

Both acidemia and alkalemia may cause neurologic signs in part due to their effects on cerebral blood flow. Acidemia, especially caused by hypoventilation, will increase cerebral blood flow and cerebrospinal fluid pressure. Carbon dioxide is thought to have a direct CNS depressant effect (CO_2 narcosis). Respiratory acidosis tends to have a greater effect than metabolic acidosis on responsiveness and the effect is most marked when onset of hypercapnia is abrupt (Greenbaum, 2011; Shannon, 2007). Various central signs such as abnormal ventilatory patterns, abnormal responsiveness, depression, and loss of consciousness may be seen. These signs are more likely to occur when acidemia is secondary to respiratory acidosis (Effros & Swenson, 2010). With slow onset of hypercapnia the resulting acidemia may be

tolerated with few signs. Severe acidemia is also thought to impair brain metabolism (Greenbaum, 2011). New evidence also points to acidosis causing neurologic injury; this is mediated by acid-sensing ion channels leading to a variety of effects including delayed ischemic neuronal death (Wang & Xu, 2011).

Alkalemia caused by hyperventilation can produce a marked (although transient) decrease in cerebral blood flow. Syncope caused by hyperventilation resulting in hypocapnia is due to the resulting reduction in cerebral blood flow. The reduction in cerebral blood flow is the rationale for using hyperventilation to treat increased intracranial pressure; however, it is now recognized that such therapy results in decreased oxygen delivery, making forced hyperventilation contraindicated in most cases. Acute respiratory alkalosis may also cause neuromuscular irritability, tetany, seizures and loss of consciousness (Greenbaum, 2011; Shannon, 2007).

There are other miscellaneous effects of acid–base imbalance. Acute metabolic acidemia can result in insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis can cause failure to thrive in neonates (Greenbaum, 2011). Emerging evidence suggests that changes in acid–base balance influence immune effector cell function. Thus, avoiding acid–base derangements can be important in the management of critically ill patients (Curley et al., 2010; Ijland et al., 2010; Kellum, 2005).

Although the strong ion balance is one determinant of acid–base balance, plasma concentrations of some electrolytes are affected by the acid–base balance. Acidemia causes potassium to move from the intracellular space to the extracellular space, thereby increasing the serum potassium concentration (Effros & Swenson, 2010). Alkalemia causes the opposite movement of potassium. The renal loss of potassium is also increased in alkalemia and decreased in acidemia. However, changes in serum potassium levels depend on the form of the acidosis (metabolic or respiratory). The specific types of metabolic acidosis, as well as several other factors, including changes in serum osmolality, changes in plasma insulin, aldosterone, and catecholamine levels all affect plasma potassium concentration (Shannon, 2007). Therefore, changes in plasma potassium concentrations are not a sensitive predictor of changes in acid–base status (Effros & Swenson, 2010; Greenbaum, 2011).

Acidemia results in an increase in plasma total and ionized calcium concentrations. Acid buffering in the bone

causes mobilization of skeletal calcium, leading to this increase (Shannon, 2007). Likewise acid buffering by albumin displaces bound calcium resulting in an increase in ionized calcium levels. In the author's experience, hypercalcemia is most marked in subacute to chronic respiratory acidosis. During alkalemia, the opposite occurs; the ionized calcium concentration decreases as a result of increased binding of calcium to albumin (Greenbaum, 2011). Also alkalemia enhances calcium deposition into bone. When there are rapid changes, the resulting decrease in ionized calcium concentration has been thought to cause the clinical signs of tetany, and seizure in humans (Greenbaum, 2011). Hypomagnesemia and hypophosphatemia have also been associated with alkalemia (Effros & Swenson, 2010; Shannon, 2007).

Although the above discussion has listed a wide variety of possible clinical signs that can be attributed to alterations of acid–base balance, it is frequently impossible to determine which signs are a direct result of acidemia or alkalemia and which are the result of the underlying disease problem leading to the acid–base imbalance. Facilitating the return of blood pH toward normal values will have a positive effect on the patient, both physiologically and clinically. Moderating the abnormality by appropriate therapeutic intervention may allow the patient to redirect resources used by compensating mechanisms to support other vital areas. However, there may be some advantage to not completely normalizing the pH. Normalizing the patient's blood work does not necessarily make the patient normal, and may in fact be harmful. For more than a decade it has been recognized that permissive acidosis results in lower mortality in humans with acute respiratory distress syndrome, in part because of the immune-modulating effects of hypercapnic acidosis. This has led to the concept of therapeutic acidosis in which the administration of CO₂ is used to induce hypercapnic acidosis for its beneficial effect (Curley et al., 2010; Ijland et al., 2010). In the face of sepsis the situation is more complicated, with hypercapnic acidosis having both positive and negative influences (Curley et al., 2010).

Interpretation of the acid–base balance

Appropriate interpretation of acid–base abnormalities requires simultaneous measurement of plasma electrolytes and arterial blood gases, as well as an appreciation

Table 8.1 Comparison of arterial and venous blood gases drawn simultaneously from a patient.

Source	Venous blood	Arterial blood
pH	7.162	7.347
Pco ₂	59.8 mmHg	28.5 mmHg
Po ₂	28.4 mmHg	92.8 mmHg
BE	−7.3 mEq/L	−7.8 mEq/L
HCO ₃ [−]	21.5 mEq/L	15.7 mEq/L
Glucose	18 mg/dL	50 mg/dL

BE, base excess.

Metatarsal artery and associated venous samples drawn within 2 minutes of each other in a foal with septic shock.

by the clinician of the physiologic adaptations and compensatory responses that occur with specific acid–base disturbances (DuBose, 2012). Although venous blood gases are often used as a surrogate for arterial values, this can be misleading. Venous pH reflects the regional metabolism of the tissues drained by the vein used whereas the arterial pH reflects respiratory compensation. With severe illness these may be very different (see Table 8.1). Interpretation of acid–base disturbances may be misleading without accurate measurements of the clinical chemistry components. Normal values for the laboratory and instruments used for the analysis also need to be considered. Because of the variation in measurements, when serial samples are analyzed, the same instruments should be used. Finally, it should be understood that although normal ranges are established for populations, the individual tends to maintain values with less variation within this normal range. This is especially true for pH values because of the strict control.

Traditional versus alternative approaches

Critically ill patients rarely have a single acid–base disorder. These patients typically manifest mixed acid–base physiology with multiple, often conflicting metabolic derangements superimposed on respiratory disease or compensation. A number of approaches are used on clinical cases first to diagnose the acid–base abnormality and then to try to understand the underlying pathologic origin of the abnormality. This section will review some of the analytical tools available to explore acid–base abnormalities and discuss their interrelationship, usefulness, and limitations. No matter which approach is used by a clinician to detect the presence of an acid–base

imbalance, all methods will point out the presence of an abnormality making the choice of approach more a matter of style than acknowledging that one approach is superior to another. However, because of the nature of the analysis, different approaches may point to different underpinnings of the problem and lead to somewhat different approaches to therapy. No matter which approach is used to try to understand the underlying pathophysiology leading to a patient’s acid–base status, no method will completely explain all derangements. The complex acid–base interactions of the various influences may even cancel each other’s effects.

All approaches recognize the contribution of volatile acid (CO₂), usually referred to as the respiratory component and volatile base (HCO₃[−]) considered part of the metabolic component. All approaches also recognize the contribution of non-volatile acids and bases to the metabolic component but traditional approaches rely on their presence being reflected in changes in HCO₃[−] instead of measuring them independently. The non-volatile components include strong ions, inorganic weak acid buffers (e.g., PO₄, SO₂), organic weak acid buffers (e.g., albumin), and other organic metabolites (e.g., lactate). The inorganic and organic weak acid buffers are often referred to collectively as the buffer base and abbreviated as “A[−]”. There are three major methods of quantifying (describing) acid–base disorders, but each differs only in assessment of the “metabolic” component. These three methods quantify the metabolic component by using HCO₃[−], standard base excess (SBE) or strong ion difference (SID), and buffer base. Although there has been significant debate about the accuracy and usefulness of each method compared with the others, all three yield identical qualitative results when used to evaluate the acid–base status of a given blood sample. However, there are differences between these three approaches in the conceptual understanding of the underlying mechanism causing the acid–base imbalance and the relative quantitative importance of the components of the acid–base disturbance (Kellum, 2005).

History of the traditional approach (see Table 8.2)

In order to understand the evolution of the traditional approach, a historical perspective is helpful. It was O’Shaughnessy who first identified the loss of HCO₃[−] from the blood as an important finding in patients dying of cholera in the London epidemic of 1831–2 (O’Shaughnessy, 1831). Thomas Latta was the first to

Table 8.2 Historical summary of acid–base analysis tools.

Analysis tool	Definition	Date proposed	Reference
Henderson equation	$[H^+] = K_1 \times [CO_2] / [HCO_3^-]$	1907	Henderson (1907)
Henderson–Hasselbalch equation	$pH = pK_1 + \log[HCO_3^-] / (S_{CO_2} \times P_{CO_2})$	1916	Hasselbalch (1916)
Van Slyke’s “buffer curve”	$\log P_{CO_2} = -pH + \log[HCO_3^-] / K_1 \times S_{CO_2}$	1921	Van Slyke (1921)
Standard bicarbonate	Concentration of bicarbonate corrected for respiratory effects	1928	Van Slyke (1928)
Buffer base	Sum of the buffer anions HCO_3^- , PO_4^{3-} and the protein anions	1948	Singer and Hastings (1948)
Base excess	Number of milliequivalents (mEq) of acid or base that are needed to titrate 1 liter of blood to pH 7.40 at 37°C while the P_{CO_2} is held constant at 40 mmHg	1963	Siggaard-Andersen (1963)
Standard base excess	Base excess corrected for hemoglobin	1977	Siggaard-Andersen (1977)
Anion gap	$(Na + K) - (Cl + HCO_3^-)$	1977	Emmett and Narins (1977)
SID (strong ion difference)	$(Na + K + Ca^{2+} + Mg^{2+}) - Cl^-$	1981	Stewart (1981)
A_{tot}	Protein anions + phosphate anions	1981	Stewart (1981)
Simplified equine SIDA	$2.25 [\text{albumin}] (\text{g/dL}) + 1.40 [\text{globulin}] (\text{g/dL}) + 0.59 [\text{phosphate}] (\text{mg/dL})$	1997	Constable (1997)

embrace O’Shaughnessy’s findings when he began treating cholera victims with intravenous HCO_3^- in that epidemic in 1832 (Latta, 1832). But it wasn’t until 1907 that Henderson coined the term “acid–base balance” and defined this process by his famous equation showing CO_2 and HCO_3^- as the key elements (Henderson, 1907). In 1916 Hasselbalch reformulated the equation using negative logarithmic pH notation and the P_{CO_2} term (Hasselbalch, 1916). The Henderson–Hasselbalch equation attempted to characterize acid–base disturbances by suggesting that changes in P_{CO_2} only reflected respiratory influences whereas changes in HCO_3^- only reflected metabolic influences. However, the Henderson–Hasselbalch equation failed to account for the influence of non-bicarbonate buffers and serum electrolytes on acid–base interpretation (Rastegar, 2009). More importantly, it suggested that P_{CO_2} and HCO_3^- are independent predictors of pH when, in fact, these variables are interdependent. Specifically, HCO_3^- will change as a result of changes in P_{CO_2} and vice versa. This is the danger when clinical assessment of the metabolic acid–base balance relies solely on this traditional Henderson–Hasselbalch concept. Bicarbonate levels, or their common surrogate total CO_2 as used on many clinical chemistry screens, will not accurately reflect the metabolic acid–base status when there are respiratory abnormalities.

Due to this interdependency, other measurements of metabolic acid–base balance independent of P_{CO_2} were

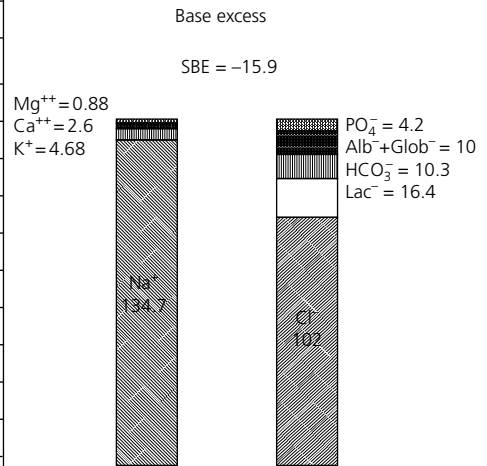
suggested such as standard bicarbonate (Jorgensen & Astrup, 1957) or the more useful base excess (BE) (Astrup et al., 1960). Both of these parameters were standardized for a P_{CO_2} of 40 mmHg and fully saturated blood. Siggaard-Andersen defined base deficit/excess as the amount of strong acid or base required to return 1 liter of whole blood to pH 7.4, assuming a P_{CO_2} of 40 mmHg, full oxygen saturation, and temperature of 37°C (Siggaard-Andersen, 1963). The influence of all buffers (bicarbonate and non-bicarbonate buffers – primarily albumin and inorganic phosphate) referred to as the “buffer base” (Singer & Hastings, 1948) was also recognized. The BE was developed to measure the change in buffer base to define the metabolic component. Although BE helped separate metabolic acid–base abnormalities from respiratory influences, it could not differentiate among the various possible sources of non-respiratory acid–base disturbances. In fact, complex situations may arise resulting in multiple metabolic influences cancelling each other and resulting in a normal BE despite significant acid–base abnormalities.

Standard base excess

Because of the pitfalls of using HCO_3^- to detect metabolic acid–base abnormalities, standard base excess (SBE) is a traditional clinical tool commonly used in evaluating the metabolic status of clinical patients (Figure 8.1). Originally BE values were derived by

Figure 8.1 Example of standard base excess (SBE). These blood values were taken from a foal in septic shock. Notice that the SBE approximates the lactate level.

Septic shock		mEq/L
pH	7.195	
Pco ₂	26.4	
SBE	-15.9 mmol/L	-15.9
Na	134.7 mmol/L	134.7
K	4.68 mmol/L	4.68
Cl	102 mmol/L	102
Ca ⁺⁺	5.31 mg/dL	2.6
Mg ⁺⁺	1.08 mg/dL	0.88
Lac	16.4 mmol/L	16.4
PO ₄	7.36 mg/dL	4.34
Alb	2.3 g/dL	7.2
Glob	2.0 g/dL	2.8
HCO ₃	10.3 mmol/L	10.3



in vitro experiments on whole blood. Although the BE calculation is accurate *in vitro*, inaccuracy exists when applied *in vivo*. This is because acute acid buffering occurs not only in blood but also throughout the whole extracellular fluid compartment, in the whole intracellular compartment (not just in the blood), and even in the bone matrix. As a result, BE becomes less accurate as acidosis increases and when there are changes in the buffer space as may occur in critical illness. When this limitation of the original BE equations was realized, the equations were modified to take into account that at least two-thirds of the extracellular fluid space that participates in buffering does not contain hemoglobin. So instead of using a normal hemoglobin value, one-third of that value was used in the formulas. The resulting value was termed the SBE. Modern blood gas machines often measure hemoglobin in the sample to use the patient's own value in the formula. When using this derived value, it is important for the clinician to know if the patient's current hemoglobin is used; both anemia and polycythemia from hemoconcentration may make the SBE value less useful if this is not taken into account. The clinician needs to realize that changes in the intravascular to interstitial fluid ratio will also decrease the value's usefulness (Kellum, 2005). These algorithms have been developed using human hemoglobin, which may lead to minor inaccuracies when used to evaluate horse acid–base status. This formula assumes a normal A_{TOT} (i.e., the total non-volatile weak acid buffer, also referred to as the buffer base), which is frequently

absent in critical patients. Wooten (2003; Kellum, 2005) developed a corrected formula (SBE_{corr}) that attempts to overcome this latter problem. It should be noted that this formula was derived using the buffering characteristics of human albumin, which are not identical to horse albumin. The equations for BE, SBE, and SBE_{corr} given here are from Kellum (2005):

$$\text{BE} = \{ \text{HCO}_3^- - 24.4 + [2.3 \times (\text{Hb} \times 1.6) + 7.7] \times (\text{pH} - 7.4) \} \times [1 - 0.023 \times (\text{Hb} \times 1.6)] \quad (8.1)$$

$$\text{SBE} = 0.9287 \times [\text{HCO}_3^- - 24.4 + 14.83 \times (\text{pH} - 7.4)] \quad (8.2)$$

$$\text{SBE}_{\text{corr}} = (\text{HCO}_3^- - 24.4) + [(8.3 \times \text{Alb} \times 0.15) + (0.29 \times \text{PO}_4 \times 0.32)] \times (\text{pH} - 7.4) \quad (8.3)$$

where Hb = hemoglobin (g/dL), HCO₃⁻ = bicarbonate (mEq/L), and PO₄ = phosphate (mg/dL).

Changes in SBE and HCO₃ frequently correlate closely, but not always. Traditionally, the difference has been ascribed to the effects of “buffering”, the argument being that strong acids (or bases), quantified by SBE, are “buffered” by plasma proteins, hemoglobin, HCO₃, and even bone. The resulting changes in HCO₃ and pH are a result of this buffering process. As explained by Stewart and confirmed experimentally by others, the fundamental physical-chemical properties of biologic solutions dictate much of this so-called “buffering”.

Beyond the traditional approach

Analysis beyond the traditional Henderson–Hasselbalch approach involves consideration of the roles of strong ions and the buffer base (Figure 8.2). Changes in both strong ions and buffer base will be reflected in changes in the Henderson–Hasselbalch equation (having effects on HCO_3^- levels); however, examining the changes themselves, rather than their reflection in changes in HCO_3^- , lends understanding to the underlying causes of the acid–base abnormality. In addition, this approach helps to explain complex situations where concurrent acidifying and alkalizing influences occur simultaneously, which cannot be detected using the traditional approach. In attempts to explain these more complex acid–base problems, methods have been developed based on a theoretical foundation of the principles of electroneutrality and recognizing the role of strong ions and plasma weak acids. These include the “anion gap” (AG), introduced by Emmet and Narins (1977) and identifying unmeasured anions, and concepts introduced by Stewart (1981) and Fencel and Leith (1993) including strong ion difference (SID) and strong ion gap (SIG).

Strong ions

Strong ions are ions that exist in solution in a completely dissociated state, maintaining their electrical charge. The degree of dissociation of substances in water determines whether they are strong acids or strong bases. Lactic acid, which has an ion dissociation constant

(pK_a) of 3.4, is virtually completely dissociated at physiologic pH and is a strong acid. Conversely, carbonic acid, which has a pK_a of 6.4, is incompletely dissociated and is a weak acid (weak ion). Similarly, ions such as Na^+ , K^+ and Cl^- that do not easily bind other molecules are considered strong ions as they exist free in solution. Major strong ions in normal extracellular fluid include Na^+ , Cl^- , K^+ , SO_4^{2-} , Ca^{2+} , and Mg^{2+} . Their contribution to a solution’s electrical charge must remain balanced by other strong or weak anions or cations. H^+ is a weak cation whose concentration changes as SID changes in order to maintain electrical neutrality. This is the basis forming the connection between SID and pH. Plasma ions such as Cu^{2+} , Fe^{2+} , Fe^{3+} , Zn^{2+} , Co^{2+} , and Mn^{2+} , which do not behave as simple ions, are assumed to be quantitatively unimportant because of their low plasma concentrations.

Electrical neutrality must always hold. Consequently, the accumulation of strong anions (Cl^- , lactate, ketones, sulfate, etc.) is the “footprint” or “ghost” left by a strong acid. When a strong acid such as lactate (Lac^-H^+) is produced, much of the H^+ is buffered (combining with a weak base) thus the electrical neutrality is preserved as anionic buffering sites are neutralized by combining with H^+ allowing the accumulation of Lac^- without changing the electrical neutrality. A small amount of unbuffered H^+ lowers the pH. The accumulation of strong anion is a reflection of the amount of acid added to the system as it is produced. We measure the

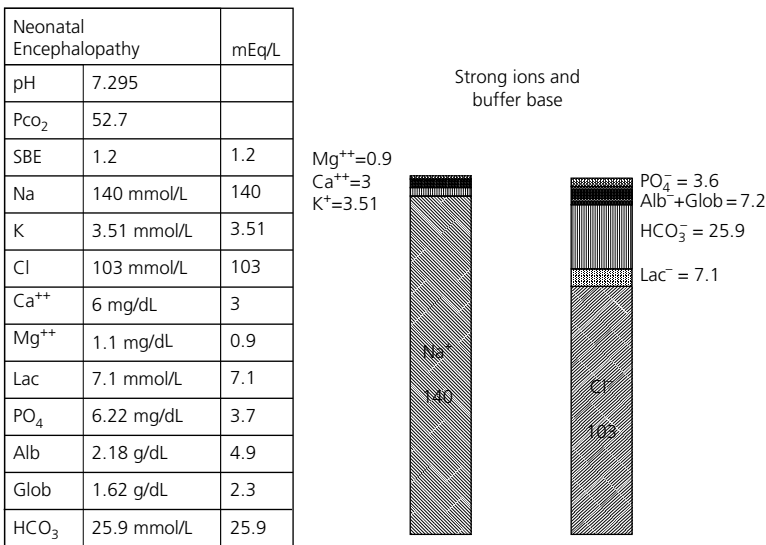


Figure 8.2 Gamblegram showing relative ratios of strong ions and components of the buffer base. Blood values from a foal with neonatal encephalopathy. SBE, standard base excess.

Lac⁻ level to determine the acid load introduced by lactate production even though it itself is a base.

Buffer base (non-volatile weak acids, A_{tot}⁻)

There are a number of substances in the body that, because of their pK_a, act as buffers. In plasma, where pH is measured, there are only two substances that act as non-volatile weak acid buffers and have concentrations great enough to produce significant acid–base disturbances when abnormal: inorganic phosphate (PO₄) and plasma protein (especially serum albumin (Alb)). Albumin, because of its multiple buffering sites available at the physiologic (and pathophysiologic) pH range, can act as a non-volatile weak acid buffer. The charge makeup of albumin is quite complex. Specifically, human albumin contains 99 residues with fixed negative charges (mainly aspartate, and glutamate) and 77 fixed positive charges (lysine and arginine) that are independent of pH in the physiologic and pathophysiologic range. Therefore each molecule of albumin has a fixed negative charge of 22 mEq/L, no matter what the plasma pH is. In addition, albumin has 16 histidine residues that react with H⁺ depending on the pH (Kurtz et al., 2008). These are the buffering sites. Therefore, albumin always has a net negative charge (–22 to –38 depending on buffering state). Normal serum globulins carry a smaller net electrical charge at pH values prevailing in plasma, which has been ignored by some investigators (Morgan et al., 2007).

The anionic contribution of albumin, globulin, and phosphate is dependent on their plasma concentrations and the pH. As they are good buffers with appropriate pK_a values and multiple buffer sites, changes in blood pH have a small effect until the pH reaches extremes. This allows calculation of the contribution of the total anionic charge of these buffers without consideration of pH, resulting in only a small error until the pH value begins to become extreme.

The following formulas have been proposed using data from humans and are useful in horses:

$$\text{Alb}^- [\text{mEq/L}] = (\text{Alb}[\text{g/dL}] \times 10) \times ((0.123 \times \text{pH}) - 0.631) \quad (8.4a) \text{ (Figge et al., 1992)}$$

Or shortcut without pH (assumes pH = 7.40):

$$\text{Alb}^- [\text{mEq/L}] = 2.8 \times \text{Alb}[\text{g/dL}] \quad (\text{Corey, 2003})$$

Note: at pH 7.0, then 2.3 × Alb; at pH 7.6, then 3.0 × Alb (Kellum, 2007a,b).

$$\text{PO}_4^- [\text{mEq/L}] = (\text{PO}_4[\text{mg/dL}] \times 0.323) \times ((0.309 \times \text{pH}) - 0.469) \quad (8.4b) \text{ (Figge et al., 1992)}$$

$$\text{Or shortcut without pH (assumes pH = 7.40): } \text{PO}_4^- = 0.58 \times \text{PO}_4[\text{mg/dL}] \quad (\text{Corey, 2003})$$

Note: at pH 7.0, then 0.55 × PO₄⁻; at pH 7.6, then 0.61 × PO₄⁻ (Kellum, 2007a,b).

The following formula was derived using data from horses:

$$\text{A}^- [\text{mEq/L}] = (2.25 \times \text{Alb}[\text{g/dL}]) + (1.40 \times \text{Glob}[\text{g/dL}]) + (0.59 \times \text{PO}_4[\text{mg/dL}]) \quad (8.5) \text{ (Constable, 1997)}$$

Anion gap (AG)

The anion gap (AG) was developed to estimate the accumulation of unmeasured anions as strong acids are produced (Emmett & Narins, 1977). The associated H⁺ combines with and thus decreases the buffer base leaving behind an unmeasured anion producing the anion gap. These strong organic acids may accumulate because of increased production such as with lactate or ketoacids, toxic ingestion, decreased renal excretion, or errors of metabolism.

$$\text{AG} = (\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3) \quad (8.6) \text{ (Emmett \& Nairns, 1977)}$$

As the underlying principle of AG is electrical neutrality AG represents the sum of charges of electrolytes not included in the equation, usually referred to as “unidentified” anions (UA) and cations (UC). In reality AG = UA – UC. UA are primarily albumin, PO₄ and organic anions (e.g., lactate) plus minor amounts OH⁻, SO₄²⁻, and CO₃²⁻. Unidentified cations (UC) are Mg²⁺, Ca²⁺, and a large number of organic cations such as amines (epinephrine, dopamine, etc.), many drugs (about 40% of all conventional drugs) plus very small amounts of H⁺. Usually UC are a minor contributor (but not always) and can be ignored. Normal AG is

Birth asphyxia		mEq/L
pH	7.009	
Pco ₂	62.4	
AG	22.8mmol/L	
Na	131 mmol/L	131
K	4.8 mmol/L	4.8
Cl	98 mmol/L	98
Ca ⁺⁺	6.58 mg/dL	3.3
Mg ⁺⁺	1.3 mg/dL	1.1
Lac	14.5 mmol/L	14.5
PO ₄	4.99 mg/dL	2.9
Alb	2.78 g/dL	6.3
Glob	1.92 g/dL	2.7
HCO ₃	15.9 mmol/L	15.9
SBE	-13.3	13.3

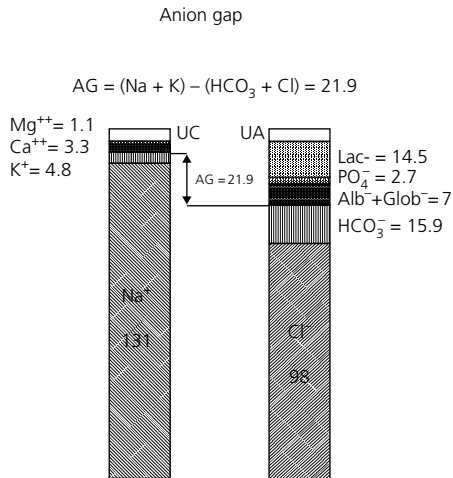


Figure 8.3 Gamblegram showing the relationship of the anion gap (AG) to components of the buffer base and strong ions. Blood values taken from a foal with birth asphyxia. SBE, standard base excess; UA, unidentified anions; UC, unidentified cations.

A⁻ (albumin, PO₄) plus small amounts of UA (lactate, sulfates, etc.), which are offset by excluded cations (Ca, Mg). An increased AG indicates an increase in UA, generally expected to be lactate in the horse but also possibly ketones, toxins, or other anions. AG was developed before measurement of lactate levels was easily achieved, primarily as a clinical aid to detect the presence and magnitude of lactic acidosis. Even though L-lactate levels are now easily measured, AG is still a valuable aid in detecting the presence and estimating the changing concentrations of other difficult to measure anions such as D-lactate, ketones, and toxins. This simple formula utilizing readily available laboratory data can be quite useful clinically. As variations in analysis techniques can cause different Cl⁻ values, normal ranges are often considered laboratory specific (Figure 8.3).

Detecting abnormalities with AG is dependent on having a normal A⁻, which is uncommon in critically ill patients. Errors in AG can come from variations in UC and UA, which are not of interest. It is unusual for UC to change significantly. Conversely UA, especially low albumin and low PO₄, can have a large effect on AG, which could mask the appearance of an organic acid of interest. High levels of PO₄, as are often found in neonates and can occur in renal failure, add to the AG; this falsely suggests the presence of other unidentified organic acids. The almost universal occurrence of hypoalbuminemia in critical patients has led to the development of a corrected AG (Figure 8.4).

$$AG_{\text{Corr}} = AG + 2.5 \times (Alb_{\text{ref}} - Alb_{\text{measured}}) \tag{8.7}$$

In neonatal foals, the almost universally low albumin (relative to adults) and variable blood PO₄ levels are problematic. Normal neonatal foals usually have a PO₄ level higher than adults, which may counterbalance the usually low albumin level in the formula. Critically ill foals can have extremely high PO₄ or occasionally very low concentrations. Without correcting for both the albumin level and PO₄ level, AG can be misleading in foals. A “corrected AG” (cAG) has been utilized to take into account the patient’s albumin and PO₄ levels, and if the lactate value is added the normal cAG is zero (this formula is designed for an acid pH):

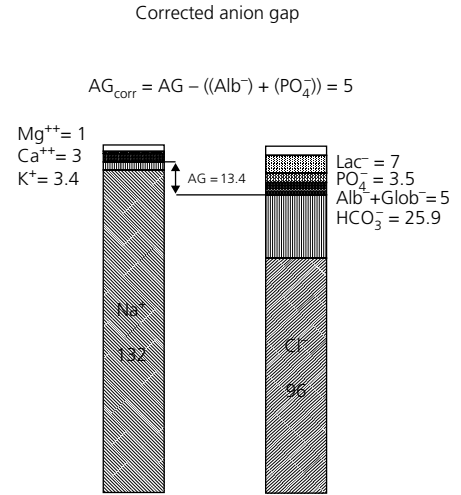
$$cAG = ((Na + K) - (HCO_3 + Cl)) - ((2 \times Alb [g/dL]) + (0.5 \times PO_4 [mg/dL])) - Lac [mmol/L] = 0 \tag{8.8} \text{ (Kellum, 2007a)}$$

The AG method does not identify acid–base abnormalities that are due to alterations in plasma free water. Additionally, the AG method does not account for the correction of chloride concentration in the setting of altered plasma free water. As a result, a hyperchloremic acidosis in the setting of a dilutional alkalosis would not be identified with an analysis using the AG method. In general AG analysis is well suited to detect the rapid increase of UA in a patient that was previously normal but is suffering from an emergent problem such as hypovolemic shock with resulting lactic acidosis. However, the AG can fail in more complex, chronic situations.

Another problem with AG is its reliance on HCO₃⁻. It does not account for changes associated with changes in

Foal after a dystocia		mEq/L
pH	7.390	
Pco ₂	42.6	
AG	13.5 mmol/L	
Na	132 mmol/L	132
K	3.4 mmol/L	3.4
Cl	96 mmol/L	96
Ca ⁺⁺	6.13 mg/dL	3
Mg ⁺⁺	1.4 mg/dL	1
Lac	7 mmol/L	7
PO ₄	4.19 mg/dL	2.5
Alb	1.28 g/dL	2.9
Glob	1.52 g/dL	2.1
HCO ₃	26 mmol/L	26
SBE	1.3	1.3

Figure 8.4 Gamblegram showing the value of the corrected anion gap (AG_{corr}). Blood values taken from a foal delivered from a dystocia at the time of birth. Note the calculated anion gap of 13.4 would be considered normal in many laboratories but is clearly abnormal when compared to the calculated corrected normal value of 5 in this foal. SBE, standard base excess.



Pco₂. To address this problem, the concept of “the delta-delta” was developed. Delta AG_{corr} (ΔAG_{corr}) is the difference between the calculated AG_{corr} and the reference AG. Delta HCO₃⁻ (ΔHCO₃⁻) is defined as the difference between the reference HCO₃⁻ and the measured HCO₃⁻. The incremental increase in AG_{corr} should be mirrored by the same incremental decrease in HCO₃⁻ so ΔAG_{corr} should equal ΔHCO₃⁻ if the AG is only a result of metabolic acidosis. But this 1:1 ratio of ΔAG_{corr} to ΔHCO₃⁻ fails to consider the role of non-bicarbonate buffers, assumes the same volume of distribution for both the conjugate base and the proton, and disregards the duration of acidosis. Taking these three conditions into account, the actual ratio is variable depending on the acid that is present and ranges from 0.8:1 to 1.8:1 for lactate and from 0.8:1 to 1:1 for ketoacids. The range of 1–1.6:1 has been used in delta–delta calculations. This range hides subtle confounding abnormalities.

AG will increase steadily as Pco₂ falls and pH rises, ultimately almost doubling. The AG increase with pH has been attributed to altered albumin and phosphate dissociation (Morgan et al., 2007). Therefore, AG is only useful in acidosis and has a number of confounding influences, which are largely eliminated with the Stewart–Fencl approach.

Strong ion difference (SID)

Peter Stewart based his approach on principles of physical chemistry keeping true to electrical neutrality, dissociation equilibriums, and mass conservation.

Although his original analysis is too cumbersome for routine use, his ideas have led to the derivation of clinically useful tools helpful in understanding the underlying cause of acid–base disturbances (Rastegar, 2009).

This approach recognizes only three independent variables: SID, concentration of weak acids (buffer base, A_{TOT}), and Pco₂. This analysis approach recognizes that all acid–base disturbances are a result of changes of these three variables, which are then reflected in changes in the dependent variables H⁺ and HCO₃⁻. These variables determine the pH, rather than merely being correlated (Kellum, 2005). Changes in Pco₂ are called respiratory acid–base disturbances, and changes in SID and/or A_{TOT} are metabolic acid–base disturbances. A_{TOT} is defined as the total amount of weak acid species in both the dissociated and the non-dissociated form, which is an independent variable whereas the amount dissociated is dependent on the pH (number of H⁺ that need buffering) and the amount of weak acid present.

The SID can be calculated as the difference of the major strong cations and strong anions: SID_A = (Na⁺ + K⁺) – (Cl⁻ + Lac⁻). When the levels of Ca²⁺ and Mg²⁺ are known they can be included to increase the accuracy of the result. In normal horses the SID is approximately 40 ± 2 (Figure 8.5). Changes in the SID will reflect the contribution of the strong ions to the acid–base balance. These changes can be quantified identifying not only whether the strong ion balance has an alkalinizing or acidifying effect, but also the magnitude of the effect. This is especially useful when there is a hyponatremia

FIRS, sepsis		mEq/L
pH	7.46	
Pco ₂	39.8	
SID	38	
Na	137 mmol/L	137
K	3.8 mmol/L	3.8
Cl	102 mmol/L	102
Ca ⁺⁺	5.11 mg/dL	2.56
Mg ⁺⁺	1.28 mg/dL	1.05
Lac	4.8 mmol/L	4.8
PO ₄	4.14 mg/dL	2.4
Alb	4.9 g/dL	11
Glob	0.76 g/dL	1.1
HCO ₃	28.6 mmol/L	28.6
SBE	4.7	4.7

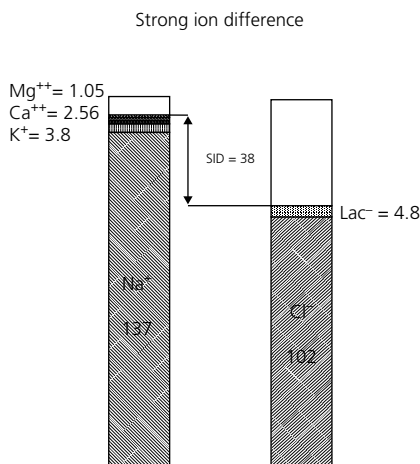


Figure 8.5 Gamblegram showing the apparent strong ion difference (SID_A). Blood values taken from a foal with FIRS (fetal inflammatory response syndrome) and sepsis. SBE, standard base excess.

and hypochloremia. In this situation, there may be a *relative* hyperchloremia (relative to sodium) despite a low chloride concentration resulting in a decreased SID. This would have an acidifying effect that might not be evident otherwise. The opposite may also be true.

Strong ion gap (SIG)

Strong ion difference can be calculated two different ways. Apparent SID (SID_A) is the difference between the identified strong cations and the identified strong anions as noted above:

$$SID_A = (Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + Lac^-)$$

Effective SID essentially includes the UC and UA in the formula but practically is calculated as the sum of the non-volatile and volatile weak acid buffer:

$$SID_E = HCO_3^- + Alb^- + Glob^- + HPO_4^- + PO_4^{2-} = (Na^+ + K^+ + Ca^{2+} + Mg^{2+} + UC) - (Cl^- + Lac^- + UA)$$

The presence of UA or UC will cause a strong ion gap (SIG):

$$SIG = SID_A - SID_E = UC - UA.$$

UA contributing to the gap may include D-lactate, formate, ketoacids, salicylates, and sulfates. Unlike AG, a normal SIG should be 0 no matter what the albumin and phosphate levels are and is not confounded by respiratory

influences on HCO₃⁻. Also, unlike AG, assuming a normal SIG=0 and no confounding UC, the SIG value will equal the amount of UA present in mEq/L.

$$SID_A = (Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + Lac^-) \tag{8.9}$$

$$SID_E = HCO_3^- + ((Alb[g/dL] \times 10) \times ((0.123 \times pH) - 0.631)) + ((PO_4[mg/dL] \times 0.323) \times ((0.309 \times pH) - 0.469)) \tag{8.10}$$

The behavior of A⁻, and more specifically albumin, differs between species and changes in pH have small effects until they become extreme. The following formula has been proposed for horses based on the behavior of horse plasma with a pH between 7.20 and 7.60:

$$SID_E = HCO_3^- + (2.25 \times Alb[g/dL]) + (1.40 \times Glob[g/dL]) + (0.59 \times PO_4[mg/dL]) \tag{8.11} \text{ (Constable, 1997)}$$

It is important to realize that neither SID_A nor SID_E are exact determinations as there will always be some unmeasured ions. Despite this limitation, in normal individuals the SIG is nearly zero. In sepsis and other critical illnesses, such as liver failure, the SIG is often increased as high as 15 mEq/L or more, reflecting an increase in UA. This SIG acidosis is the primary origin of the otherwise unexplained acidosis often encountered in critical cases. The chemical nature of UA is largely

unknown but likely the UA are from multiple sources that vary from one case to another. D-Lactate, unlike L-lactate, is not routinely measured and may be a significant contributor in some cases. Low molecular weight anions associated with intermediary metabolism may comprise up to one-half of the UA; these include ketones or sulfates induced by inflammation or other pathology, or that accumulate in the face of renal and liver dysfunction. Exogenously administered unmeasured anions (notably gelatins or acetate, citrate, and gluconate) also may contribute as UA, especially in the face of liver dysfunction. During sepsis, acute-phase proteins released from the liver, other inflammatory proteins, cytokines, and chemokines may also be significant contributors; hepatic or renal dysfunction may decrease their clearance. This may explain the connection between SIG acidosis and a poor prognosis, as the presence of these substances reflects both the magnitude of the inflammatory response and the presence of organ dysfunction. Not all metabolic acidoses have equal significance (Kellum, 2007a). The prognostic significance of a SIG acidosis in lactic acidosis is far worse than the same degree of acidosis originating from other causes such as hyperchloremia.

One flaw in the SIG is the inability to detect and account for UC. Most clinicians assume the contribution of UC is too small to consider. This may not always be true. Organic cations are numerous, but in normal horses they are not present in high amounts. Endogenous organic cations comprise many substances including amines such as epinephrine and dopamine and some amino acids. Exogenous cations are also common. Forty percent of commonly used drugs are cations. Many xenobiotics including toxins and other environmental substances are also cationic. At times critically ill neonatal foals have a negative SIG indicating a predominance of UC.

The SID and SIG can be calculated without a blood gas analysis, allowing an appreciation of the metabolic acid–base state in any case with information obtained solely from a chemistry panel. However, in order to fully evaluate the importance of the metabolic changes, the blood pH and P_{aCO_2} need to be considered. Arterial samples should be used whenever possible in order to determine whether the metabolic changes are primary or appropriate compensation for respiratory abnormalities; similarly, they are used to detect if respiratory compensation is appropriate or if

respiratory abnormalities are primary or coexisting. This perspective is necessary before therapeutic intervention is considered.

Modified base excess method

Various attempts have been made to combine the traditional approach with the Stewart approach to improve the understanding of the origin of the metabolic acid–base disturbance. SBE does not help to differentiate concurrent acid–base disorders leaving it less than ideal in complex situations. Gilfix and colleagues (1993) attempted to address this shortfall by combining the BE analysis and Stewart’s approach into a more encompassing quantitative analysis. This analysis recognizes four conditions that can create metabolic acid–base disturbances: (i) a free water deficit or excess; (ii) changes in chloride concentration; (iii) changes in A^- ; and (iv) the presence of organic UA. The following formulas describe the derivation of these four components of SBE:

$$BE_{\text{measured}} = BE_{\text{fw}} + BE_{\text{Cl}} + BE_{\text{alb}} + BE_{\text{UA}} \quad (8.12) \text{ (Gilfix et al., 1993)}$$

where BE_{measured} is the BE derived from the blood gas analysis; BE_{fw} is the free water component; BE_{Cl} is the contribution by Cl; BE_{alb} is the contribution by albumin; and BE_{UA} is the contribution by UA. These terms are calculated as follows:

$$BE_{\text{fw}} [\text{mEq/L}] = 0.3 \times (\text{Na}_{\text{measured}} - \text{Na}_{\text{ref}})$$

$$BE_{\text{Cl}} [\text{mEq/L}] = \text{Cl}_{\text{ref}} - \text{Cl}_{\text{Corr}}$$

$$BE_{\text{alb}} (\text{mEq/L}) = 3.4 \times (\text{Alb}_{\text{ref}} - \text{Alb}_{\text{measured}})$$

So:

$$BE_{\text{UA}} = BE_{\text{measured}} - (BE_{\text{fw}} + BE_{\text{Cl}} + BE_{\text{alb}})$$

This approach allows a better understanding of the contribution of these influences on acid–base abnormalities so that each can be addressed separately in the therapeutic plan. But the reliance on normal values for Na, Cl, and albumin confounds the results. While individuals may maintain levels of these substances within a narrow range, there is no satisfactory method of choosing a normal value for the individual patient from the population normal range. Using different normal

values within the expected range can greatly affect the result limiting the clinical usefulness of this type of analysis.

Metabolic acidosis

Metabolic acidosis is by far the most common and important acid–base abnormality in all equine patients whether they are adults, juveniles, or neonates (Table 8.3). Lactate is the most important metabolic acid and beyond its effect on the acid–base balance, its accumulation has important prognostic significance.

Lactic acidosis

L-Lactate is an important metabolite in normal physiologic conditions. Approximately 1500 mmol of L-lactate are produced daily, primarily from skeletal muscle, skin, brain, intestine, and red blood cells (Rachoin et al., 2010; Vernon & LeTourneau, 2010). Levels remain low as clearance keeps pace with production.

Hyperlactatemia – accumulation of excess lactate in the blood – is the most common cause of acidosis in the horse. In severe illness, L-lactate production occurs with hypoxia secondary to hypoxemia, hypoperfusion, or deficient oxygen-carrying capacity (anemia). In a low oxygen tension state, pyruvate does not enter the mitochondria for oxidative phosphorylation. Hypoxia is known to inhibit the pyruvate dehydrogenase (PDH) complex involved in aerobic breakdown of pyruvate to acetyl coenzyme A (Vernon & LeTourneau, 2010). Lactic

acidosis caused by cell hypoxia has been referred to as type A lactic acidosis. Hyperlactatemia without tissue hypoxia has been referred to as type B lactic acidosis. There are a number of causes of type B lactic acidosis, which commonly occur in sepsis. Any tissue undergoing a significant inflammatory response will be a source of lactate. Leukocytes produce large amounts of lactate during phagocytosis or when activated in sepsis in the presence of normal oxygen levels (Vernon & LeTourneau, 2010). Other causes of type B lactic acidosis include thiamine deficiency, hypermetabolism/catabolism of sepsis, β_2 -adrenergic stimulation of the Na/K pump, and increased muscle activity as occurs in neonatal foals with seizures. Also, in sepsis the enzyme regulating lactate metabolism, pyruvate dehydrogenase kinase, increases in activity. This enzyme inactivates the pyruvate dehydrogenase (PDH) complex, which metabolizes pyruvate. Pyruvate and lactate may accumulate as a result, independent of any effect of diminished tissue perfusion (Rachoin et al., 2010). Catecholamine-induced and sepsis-induced alterations in glycolysis and mitochondrial function, and increased pyruvate production, combined with increased glucose entry into cells, can also lead to hyperlactatemia (Rachoin et al., 2010).

Decreased lactate clearance can be mediated by inflammatory mediators, hypoperfusion of the liver and kidneys, and liver or kidney dysfunction, and may contribute to hyperlactatemia (Vernon & LeTourneau, 2010). Lactate clearance occurs principally in the liver (60%) with important contributions from the kidney (30%) and to a lesser extent other organs (heart and skeletal muscle) (Vernon & LeTourneau, 2010). Renal lactate clearance is primarily through metabolism and not excretion (Rachoin et al., 2010). Due to reabsorption in the proximal convoluted tubule, urinary excretion of lactate is normally under 2% but can rise to 10% with markedly increased lactate concentrations once the renal threshold is exceeded (approximately 5 mmol/L) (Boyd & Walley, 2008; Vernon & LeTourneau, 2010).

Available data indicate that lactate itself is not necessarily harmful and is shuttled to tissues during stress states as a carbon backbone energy fuel. When lactate levels are increased in the blood, it may be more of an indicator of an underlying stress state and secondary metabolic disruption than the direct cause of pathogenesis (Rachoin et al., 2010; Vernon & LeTourneau, 2010). Although lactic acid accumulation is a marker of severe illness, it also potentially plays a protective role

Table 8.3 Causes of metabolic acid–base disturbances.

Abnormality	Acidosis	Alkalosis
Abnormal SID		
UA (e.g., D-lactate, keto acids)	↓SID ↑[UA ⁻]	–
UC (e.g., organic cations)	–	↑SID ↑[UC ⁺]
Free water excess or deficit	Water excess = dilutional	Water deficit = contraction
	↓SID + ↓[Na ⁺]	↑SID ↑[Na ⁺]
Chloride	↓SID ↑[Cl ⁻]	↑SID + ↓[Cl ⁻]
Abnormal A_{TOT}		
Albumin [Alb]	↑[Alb] (rare)	↓[Alb]
Phosphate [Pi]	↑[Pi]	↓[Pi]

A_{TOT}, total amount of weak acid species in both dissociated and non-dissociated forms; SID, strong ion difference; UA, unidentified anions; UC, unidentified cations.

especially in providing energy for the heart in the face of severe hypoglycemia (Rachoin et al., 2010). During periods of stress other organs, notably the brain, also use lactate preferentially as an energy substrate, reflecting its beneficial effects (Rachoin et al., 2010). The usefulness of increased lactate production routinely seen in sepsis may thus represent multiple adaptive processes aimed at improving the delivery of energy substrates to vital tissues (Rachoin et al., 2010).

The influence of L-lactate on the acid–base balance can best be judged by examining the SID_A . The normal SID_A is approximately 40 mEq/L. The degree to which the SID_A decreases below 40 when lactate (mmol/L) is included in the formula reflects the acidifying effect of lactate. Leaving the lactate value out of the SID_A formula will indicate what the acid–base balance will be after clearance of the lactate. Often in foals this exercise will uncover a concurrent underlying SID alkalosis. If the lactate value has not been measured, it may be a major contributor to the SIG. In cases of hyperlactatemia, the SIG gap is a good estimate of the unmeasured acid. It should also be noted that lactate (mmol/L) will have a direct effect on SBE. Again, as with SID_A , lactate will contribute to the SBE value millimole for millimole. So subtracting the lactate value from the SBE will both indicate the influence of the lactatemia on the acid–base balance and may help uncover concurrent problems. Patients with a hyperlactatemia will also have low HCO_3 levels and increased AG but since the relationship is not direct less can be learned by examining these values.

It should also be noted that the presence of hyperlactatemia does not necessarily mean an acidosis is present. It is not unusual for a foal with mixed acid–base abnormalities to have an overall metabolic alkalosis despite having a moderate hyperlactatemia.

Therapy for lactic acidosis

Interventions to correct lactic acidosis should be focused on correcting the underlying etiology. Insuring adequate perfusion and oxygen delivery and combating sepsis are the most important and indeed the most effective therapies. Sodium bicarbonate therapy is not recommended. Administration of sodium bicarbonate may significantly raise the pH and serum bicarbonate as well as the partial pressure of carbon dioxide, but this effect is transient. This therapy does not translate into improved hemodynamics or augmented sensitivity to catecholamines (Boyd & Walley, 2008). Indeed, sodium

bicarbonate administration in lactic acidosis has been shown to be detrimental in other species. Studies evaluating sodium bicarbonate in lactic acid fail to show convincing benefit and raise serious questions about its detrimental effects (Rachoin et al., 2010).

Unidentified anions (UA)

Traditionally L-lactate has been the main unidentified anion. In fact the AG analysis was developed to identify the presence of lactate. Today, with routine availability of lactate assays, L-lactate is accounted for except in cases with laboratory failures. In herbivores, D-lactate continues to be a major UA. Other major endogenous UA include ketoacids, volatile fatty acids (VFAs), and sulfates. Other sources of organic UA are ingested organic acids such as salicylates, methanol, and ethylene glycol.

The presence of UA/UC is discovered through the realization that the numbers don't "add up" and there is a "gap" (AG or SIG). Unaccounted changes in other major players, especially hypoalbuminemia, hypoglobulinemia, or the occurrence of UC, can mask the presence of UA by making it appear that the numbers do add up as they exert an opposite effect. This is the reason to use AG_{corr} or SIG and part of the reason a significant proportion of acid–base disturbances defy a full explanation. Many patients with severe disease will have at least some UA as reflected by the presence of a SIG of 4–8. The source of the UA in these cases may be D-lactate or metabolites accumulating during sepsis such as ketones, sulfates, acute-phase proteins, other inflammatory proteins, cytokines, chemokines, and other mediators. Exogenously administered unmeasured anions (notably gelatins or acetate, citrate, and gluconate, especially in the face of abnormal liver metabolism) and toxins also may contribute to UA.

Therapy for UA acidosis

Like lactic acidosis, the underlying cause for the accumulation of UA should be addressed rather than trying to correct the acidosis with the use of sodium bicarbonate (Figures 8.6 and 8.7). Improving clearance of the UA by improving liver and renal perfusion can also be important in addressing a SIG acidosis.

Hyperchloremic acidosis

A hyperchloremic metabolic acidosis can occur in two ways. First, Cl can be added to the circulation, either by way of an exogenous source (e.g., saline) or internal

Intrauterine distress birth asphyxia		mEq/L
pH	6.791	
Pco ₂	59.6	
SID _A	62.9	
SID _E	32.9	
SIG	30	
Na	142 mmol/L	142
K	4.13 mmol/L	4.13
Cl	88 mmol/L	88
Ca ⁺⁺	5.49 mg/dL	2.74
Mg ⁺⁺	2.49 mg/dL	2.04
Lac	?? mmol/L	??
PO ₄	27.8 mg/dL	16.4
Alb	2.97 g/dL	6.7
Glob	1.73 g/dL	2.4
HCO ₃	9.2 mmol/L	9.2
SBE	-22.5 mEq/L	-22.5

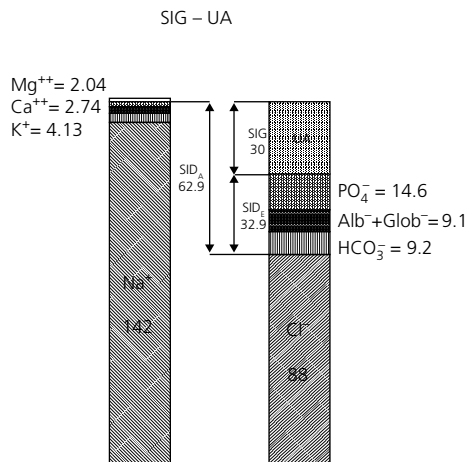


Figure 8.6 Gamblegram showing strong ion gap (SIG) and quantification of UA (unidentified anion). Blood values taken from a foal with intrauterine distress and birth asphyxia. In this case the lactate level was above the measuring limit of the analysis technique. It is likely none of the UA was lactate. SBE, standard base excess; SID_A, apparent strong ion difference; SID_E, effective strong ion difference.

Neonatal encephalopathy		mEq/L
pH	7.088	
Pco ₂	45.9	
SID _A	43	
SID _E	34.3	
SIG	8.7	
Na	135 mmol/L	135
K	4.23 mmol/L	4.23
Cl	81 mmol/L	81
Ca ⁺⁺	4.23 mg/dL	2.12
Mg ⁺⁺	1.23 mg/dL	1.06
Lac	18.6 mmol/L	18.6
PO ₄	20.53 mg/dL	12.1
Alb	2.89 g/dL	6.5
Glob	1.71 g/dL	2.4
HCO ₃	14 mmol/L	14
SBE	-15.2 mEq/L	-15.2

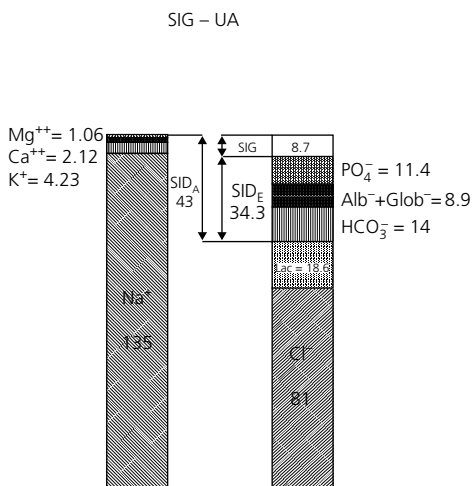


Figure 8.7 Gamblegram showing strong ion gap (SIG) and quantification of UA (unidentified anion). Blood values taken from a foal with neonatal encephalopathy. SBE, standard base excess; SID_A, apparent strong ion difference; SID_E, effective strong ion difference.

shifts (e.g., from the red cell). Second, Cl can be retained or reabsorbed while water and other ions (e.g., Na) are excreted, so that the relative concentration of Cl as compared to (Na + K) increases. Hyperchloremia is a cause of SID_A acidosis and its magnitude and importance are best judged by examining the SID_A (Kellum, 2005). The smaller the SID_A (<40) the more important the contribution of hyperchloremia to the acidosis. The hyperchloremia will also be reflected in an equal molar decrease in SBE. Hyperchloremia is usually caused by

gastrointestinal or renal disease. There is a small population of patients who have hyperchloremia that cannot be explained by renal or gastrointestinal mechanisms.

Gastrointestinal causes of hyperchloremia

Any process where Na is lost without Cl, such as severe diarrhea, will reduce the SID leading to a hyperchloremic acidosis. For example, in diarrhea, bicarbonate loss is greater than chloride loss because of failure of the

Cl/bicarbonate exchange. This will favor development of hyperchloremia. Accompanying this is extracellular volume contraction, which stimulates renal retention of sodium with chloride, because the need to conserve water by absorbing all available Na overrides the need to lose Cl in these circumstances. This will also lead to the development of hyperchloremic metabolic acidosis. In diarrhea, absorption of NH_4^+ generated by gut bacteria may also contribute to the acidosis as Cl is reabsorbed as the accompanying anion (Effros & Swenson, 2010).

The scavenging of all available Cl in cases where diarrhea results in hypovolemia as noted above can lead to a clinical picture that closely mimics renal causes of hyperchloremia, such as tubular acidosis. These clinical entities can be confused until the patient becomes volume replete with appropriate fluid therapy. Final judgment of which problem is leading to the hyperchloremia cannot be made until the kidneys no longer need to maximally conserve fluid.

Renal causes of hyperchloremia

Although the kidneys excrete many fixed acids, control of Cl reabsorption/excretion is the major renal acid–base-balancing mechanism. As a compensatory response to alkalosis, Cl is preferentially retained by the kidney. Change in Cl concentration relative to Na leading to change in SID_A is the major renal acid–base compensatory mechanism. As the normal diet usually consists of a balance of Na and Cl, the kidneys can retain or excrete the surplus Cl depending on acid–base needs. With disease, the tubular cells responsible for the regulation of Cl excretion may fail and under some circumstance may be responsible for hyperchloremic acidosis. This tubular dysfunction may be seen in the chronic stages of renal failure or in a complex of diseases causing tubular cell dysfunction in the absence of renal pathology, which is referred to as renal tubular acidosis.

Renal tubular acidosis (RTA)

Hyperchloremic acidosis is the cardinal sign of RTA, which is a sporadic disease found in horses (Ring et al., 2005; Rocher & Tannen, 1986). RTA is a collection of genetic and acquired renal tubular disorders involving proton and bicarbonate transporters as well as chloride and sodium transporters (Bagga & Sinha, 2007; Ring et al., 2005). Three types of RTA have been described in humans: proximal RTA (type 2), distal RTA (type 1), and hyperkalemic distal RTA (type 4) (Hemstreet, 2004).

Only proximal (type 2) and distal (type 1) RTA have been described in horses (Arroyo & Stampfli, 2007).

Proximal RTA (type 2) is characterized by impaired proximal recovery of bicarbonate, thought to be a Cl transporter defect. This may be combined with other proximal tubular defects referred to as Fanconi syndrome (defective reabsorption of glucose, amino acids, electrolytes, and organic acids) (Bagga & Sinha, 2007; Hemstreet, 2004; Ring et al., 2005; Rocher & Tannen, 1986). Proximal RTA is characterized by bicarbonaturia, with a fractional bicarbonate excretion greater than 15% while on bicarbonate replacement therapy (Bagga & Sinha, 2007; Ring et al., 2005). In untreated cases, the urine is usually acidic as plasma bicarbonate drops low enough for reabsorption to keep pace with the low filter load. Treatment may be difficult because administered base is often excreted at such a high rate that the desired normalization is not achieved. The acidosis in proximal RTA can be viewed in the conventional manner as loss of bicarbonate, or from the physicochemical approach to acid–base balance as the retention of chloride resulting in a hyperchloremic acidosis (decreased SID_A) (Ring et al., 2005).

Distal RTA (type 1) is characterized by impaired ability to acidify the urine in the distal tubules (Rocher & Tannen, 1986). With distal RTA ammonium (NH_4^+) ions are not excreted in amounts adequate to keep pace with a normal rate of acid production (Bagga & Sinha, 2007; Ring et al., 2005). Again the problem may be traced to a Cl transporter abnormality. Distal RTA is recognized by the inability to decrease urine pH below 5.5 in spite of metabolic acidosis; it is also characterized by a low urine Pco_2 after bicarbonate loading indicating a lack of distal hydrogen ion secretion (Bagga & Sinha, 2007; Ring et al., 2005). In humans, nephrocalcinosis and nephrolithiasis frequently occur secondary to this condition because of hypercalciuria.

Renal tubular acidosis can occur as a primary (persistent or transient) or secondary problem. In humans, secondary RTA occurs as a result of a great number of other diseases, exposure to certain drugs and toxins, a variety of genetic defects of carrier systems in the renal tubular cells, or structural disruptions of renal tubules caused by trauma or other primary renal diseases (Ring et al., 2005). Several drugs commonly used in horses have been reported to cause RTA in humans including aminoglycosides, trimethoprim potentiated sulfa drugs, carbonic anhydrase inhibitors, non-steroidal anti-inflammatory

drugs, and tetracyclines (when outdated or degraded) (Arroyo & Stampfli, 2007; Firmin et al., 2007; Hemstreet, 2004). The time frame for development and recovery from drug-induced RTA is variable between individuals but may begin within a week of exposure to the drug and can resolve as quickly as 3–4 days after discontinuing the drug (Hemstreet, 2004).

Foals with RTA usually are presented with lethargy, failure to thrive, growth retardation, generalized weakness, ataxia, anorexia, colic, constipation, tachycardia, tachypnea, polyuria, and polydipsia (Arroyo & Stampfli, 2007; Bagga & Sinha, 2007). The signs may be quite vague. Any foal found to have a hyperchloremic acidosis (decreased strong ion difference, normal anion gap) with otherwise normal renal function and without possible GI or other origin hyperchloremia (such as treatment with large volumes of saline), should be suspected of having RTA.

Acidosis of progressive renal failure

Hyperchloremia without hyperkalemia is characteristic of many renal diseases associated with loss of renal tissue and a decrease in the glomerular filtration rate. Retention of acid in these patients is attributable to a decrease in the ability of the kidneys to excrete NH_4^+Cl^- . In these cases the decline in serum bicarbonate is relatively modest, but the chronic acidosis is associated with bone reabsorption, insulin resistance, and protein catabolism (Effros & Swenson, 2010).

Identifying the kidneys as the source of the hyperchloremia

If the origin of the hyperchloremic acidosis is extrarenal and renal function is normal, large amounts of chloride would be expected to be excreted in the urine with NH_4^+ to excrete the acid load. The urine strong ion difference (urine Na + urine K – urine Cl), which normally is positive (normal near 80) will be low (usually negative). Failure to excrete chloride in the urine in the face of acidosis confirms renal disease.

Saline infusion

Large volumes of normal saline infusion will produce a hyperchloremic acidosis. Take, for example, a normal patient (Na 140, K 5, Cl 100, SID_A 45) receiving a bolus of saline (Na 154, K 0, Cl 154, SID_A 0) equal to 20% of its ECF. The new values in theory would be: Na 142, K 4.17, Cl 109, and SID_A 37. It is the volume and the SID_A of the

fluid that result in the change. To illustrate this, giving 0.5 L of 1.8% NaCl (Na 308, K 0, Cl 308, SID_A 0) will result in Na 163, K 3.8, Cl 125, and SID_A 42. So hypertonic saline will result in less acidosis than normal saline if less volume is given but the administered Na and Cl remain constant. This type of theoretical example does not take into account the alkalizing effect of diluting the buffer base (albumin, globulin, phosphorus, which are acids) with the fluid administration (Guidet et al., 2010).

Other causes of hyperchloremia

A hyperchloremic acidosis can also be induced by increased chloride salt administration in the form of saline ($\text{SID}_A=0$), lactated Ringer's solutions ($\text{SID}_A=54.6$ before catabolism of lactate but 26.5 after), or total parenteral nutrition (TPN) infusions. In sepsis there are occasional patients with hyperchloremic acidosis that cannot be explained by traditional sources. It has been hypothesized that this Cl originates from intracellular and interstitial compartments as a result of the partial loss of the Donnan equilibrium that is caused by albumin exiting the intravascular space. This speculation is unproven (Gunnerson et al., 2006; Kellum, 2005; Kellum et al., 2004).

Therapy for hyperchloremia

Primary hyperchloremia is best approached therapeutically by administration of NaHCO_3 . In the traditional view this is bicarbonate replacement therapy. In the view of modifying the strong ion difference, this therapy results in the administration of Na without Cl, producing a gradual increase in the strong ion difference. When the cause of the hyperchloremia is distal RTA, correction is often accomplished using as little as 2–4 mEq/kg/day of sodium bicarbonate. When proximal RTA is the cause much larger amounts of sodium bicarbonate are needed (e.g., up to 20 mEq/kg/day) as this condition is much more refractory. When the cause of the hyperchloremia is extrarenal, correction may be accomplished with appropriate balanced crystalloid therapy without special consideration of the hyperchloremia. If sodium bicarbonate is used it should be titrated to effect.

Dilutional acidosis

Changes in free water content will change SID_A . As free water dilutes the strong ion concentrations, the SID_A will decrease resulting in a metabolic acidosis. Changes in free water are reflected by changes in sodium

concentration. Any process that leads to dilution of the total number of ions will cause an acidosis, including infusion of mannitol (before the diuresis), hyperglycemia, or the increase of any osmotically active particle that may increase the volume of extracellular water without changing the net charge.

Because of this free water effect, it may be difficult to tell how much the abnormal SID is due to changes in free water and how much is due to changes in the relative concentrations of Na and Cl. To address this problem a Cl value corrected for free water can be used:

$$Cl_{\text{Corr}} = (Na_{\text{ref}} / Na_{\text{measured}}) \times Cl_{\text{measured}}$$

The same correction can be used on all the strong ions used. The difference between SID calculated with all measured values and the SID calculated with all corrected values (and the reference Na) will indicate how much of the acidosis is from free water. A disadvantage of this technique is that the calculations will vary depending on what value is selected as the normal Na value. It should be noted that the effect is from free water excess or deficit and will not be seen with fluid overload of strong ion balanced fluid. Fluid overload will also have a dilutional effect on the buffer base (albumin, globulin, and phosphate) – these are acids having a modulating effect on the strong ion acidosis and changes in the SIG. Unlike the dilutional effect on the SID_A , the effect on the buffer base will occur no matter what the composition of the diluting fluid (Guidet et al., 2010).

Therapy

As the magnitude of the acidosis caused by dilution is usually quite small, therapy beyond avoiding unnecessary fluid loading, especially in the face of renal compromise, is not usually necessary. However dilution rarely occurs in isolation.

Buffer base concentrations

The buffer base, also referred as A_{TOT} is the total amount of weak acid species in both the dissociated and the non-dissociated form. The major contributors to the buffer base in plasma are albumin, globulin, and phosphate. Increase in weak acid concentration, such as occurs with hyperphosphatemia of renal failure and hyperproteinemia of hemoconcentration, will contribute to a metabolic acidosis. Each g/dL of albumin contributes

2.25 mEq/L of anion, each g/dL of globulin 1.4 mEq/L of anion, and each mg/dL inorganic phosphate 0.59 mEq/L of anion; taken together, especially in the face of unusually increased amounts, they will have a significant influence on the acid–base status of the patient.

Therapy

Treatment is focused on the underlying cause of the hyperproteinemia or hyperphosphatemia rather than directly at modifying their blood levels.

Metabolic alkalosis

Primary metabolic alkalosis is less common in horses than metabolic acidosis. It is more commonly involved in compensatory responses. But critically ill horses with complex underlying abnormalities leading to acid–base abnormalities often have alkalizing influences as well as acidifying influences. (see Table 8.3).

Hypochloremia

Although the kidneys excrete many fixed acids, control of Cl reabsorption/excretion is the major renal acid–base balancing mechanism. As a compensatory response to acidosis, Cl is preferentially excreted by the kidney. Change in Cl concentration relative to Na, leading to change in SID, is the major renal compensatory mechanism. As the normal diet usually consists of a balance of Na and Cl the kidneys can retain or excrete the surplus Cl depending on acid–base needs.

Any process that removes chloride without sodium, such as gastric reflux with pyloric obstruction or a chlo-riuresis, as with furosemide therapy, can lead to a hypochloremic alkalosis. Anything leading to a net loss of free water over sodium and chloride such as with a diuresis induced by hyperglycemia or use of diuretics may cause a contraction alkalosis. In this case, even though the absolute concentration of chloride will be high, the Cl concentration will not increase as rapidly as the Na concentration leading to a relative hypochloremia and an alkalosis.

Therapy

If the hypochloremia is compensatory, it should not be corrected. If it appears primary and there is evidence of volume depletion, the fluid/chloride deficit should be corrected with normal saline. If the hypochloremic

metabolic alkalosis is associated with hypokalemia and total body potassium deficits, correcting the deficit with potassium chloride (KCl) will also aid in reversing the alkalosis. As the potassium deficit will be predominantly intracellular, all but a small fraction of retained potassium ends up within the cells during correction. The net effect of KCl administration is that the retained strong anion (Cl^-) stays extracellular, whereas most of the retained strong cation disappears into the intracellular space. This will reduce plasma SID.

Unidentified cations (UC)

The presence of UC is much less common than UA. They include endogenous organic cations such as amines and exogenous organic cations such as ingested toxins and toxic levels of drugs (almost half of the organic drugs we use are cations). It is very rare for UC to be found in concentrations high enough to confound acid–base analysis; however, in equine neonatology endogenous UC can occur at significant levels. For the most part they remain unidentified, but can contribute to an alkalosis in critically ill neonates.

The presence of UC is discovered by the realization that the numbers don't "add up" and there is a "gap" (SIG). Unaccounted changes in other major players, especially hyperproteinemia or hyperphosphatemia, can mask the presence of UC; their presence makes it appear that the numbers do add up as they exert an

opposite effect. As the levels of UC are usually much lower than those of UA, it is likely that in many cases the presence of UC is underappreciated. The counterbalancing effect of the presence of UC and UA cannot be detected using the analytical methods developed so far. This is part of the reason why a proportion of acid–base disturbances in our patients defy our efforts to fully explain them (Figure 8.8).

Contraction alkalosis

Changes in free water content will change SID. A free water deficit causes a metabolic alkalosis by increasing the SID through a relative increase in concentration of all strong ions. Changes in free water are particularly reflected by changes in sodium concentration. Because of this free water effect, it may be difficult to tell how much the abnormal SID is due to changes in free water and how much due to changes in the relative concentrations of Na and Cl. To address this problem a Cl value corrected for free water can be used:

$$\text{Cl}_{\text{corr}} = (\text{Na}_{\text{ref}} / \text{Na}_{\text{measured}}) \times \text{Cl}_{\text{measured}}$$

The same correction can be used on all the strong ions used. The difference between SID calculated with all measured values and the SID calculated with all corrected values (and the reference Na) will indicate how much of the alkalosis is from a free water deficit.

FIRS, sepsis		mEq/L
pH	7.361	
Pco ₂	68.3	
SID _A	39.6	
SID _E	50.6	
SIG	-11	
Na	137 mmol/L	137
K	3.73 mmol/L	3.73
Cl	102 mmol/L	102
Ca ⁺⁺	4.62 mg/dL	2.31
Mg ⁺⁺	1.03 mg/dL	0.84
Lac	1.3 mmol/L	1.3
PO ₄	6.75 mg/dL	3.98
Alb	1.82 g/dL	4.1
Glob	2.48 g/dL	3.5
HCO ₃	39.1 mmol/L	39.1
SBE	13.1	

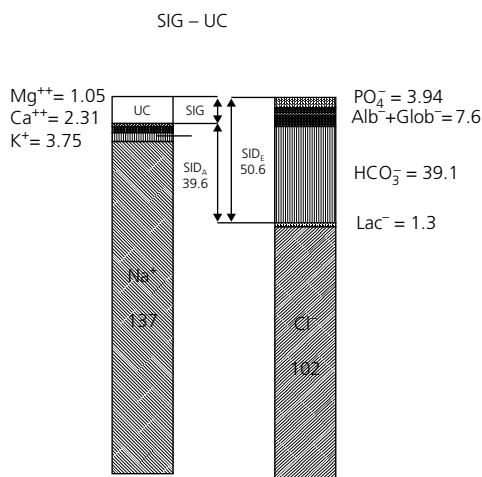


Figure 8.8 Gamblegram showing strong ion gap (SIG) and quantification of UC (unidentified cation). Blood values taken from a foal with FIRS (fetal inflammatory response syndrome) and sepsis. SBE, standard base excess; SID_A, apparent strong ion difference; SID_E, effective strong ion difference.

Albumin/phosphate concentrations

A_{TOT} is defined as the total amount of weak acid species in both the dissociated and the non-dissociated form. The major contributors to A_{TOT} in plasma are albumin and phosphate. Decreases in weak acid concentration, such as hypoproteinemia (especially hypoalbuminemia), are often present in critical patients contributing to a metabolic alkalosis. Neonates are born with low albumin concentrations but concurrently high PO_4 concentrations relative to adult horses. The two balance each other well until foals become catabolic because of neonatal illness. Albumin is an efficient buffer largely because of the multiple buffering sites on each molecule. Thus its effectiveness as a buffer is maintained at quite low concentrations. Only at the most extreme levels of hypoalbuminemia will its buffering abilities be lost. Preservation of acid buffering is not a strong indication for plasma replacement therapy in cases of hypoalbuminemia.

Respiratory acidosis

Respiratory acidosis is marked by hypercapnia, usually due to inadequate pulmonary excretion of CO_2 . Hypercatabolism induced by sepsis, leading to increased CO_2 production, may also contribute. If not supplemented with oxygen therapy, hypoxemia will occur simultaneously. Increases in the HCO_3^- concentration (approximately 0.1 mEq/L for each mmHg increase in P_{CO_2}) occurs within 5 to 10 minutes secondary to the equilibrium of CO_2 with HCO_3^- influenced by the law of mass action in the presence of carbonic anhydrase. Plasma $[H^+]$ increases by approximately 0.75 nEq/L for every mmHg increase in P_{CO_2} . The increase in HCO_3^- should not be viewed as an increase in buffer but rather the reflection of the transformation of a volatile acid (P_{CO_2}) into a non-volatile acid (H^+). Plasma potassium concentration increases by approximately 0.1 mEq/L for every 0.1 decrease in pH as a result of intracellular acid buffering. Plasma phosphate concentration also increases slightly and plasma chloride and lactate concentrations decrease slightly. The decrease in lactate is thought to be secondary to the increased intracellular acidosis inhibiting 6-phosphofructokinase interfering with glycolysis.

After 3 to 5 days, renal conservation and generation of HCO_3^- increase (approximately 0.3–0.4 mEq/L for each mmHg increase in P_{CO_2}) accompanied by increased renal excretion of Cl, resulting in a compensatory

hypochloremic alkalosis. With compensation, plasma $[H^+]$ only increases by approximately 0.3 nEq/L for every mmHg increase in P_{CO_2} . Compensatory changes will not completely restore the acid–base balance. When the hypercapnia resolves, a post-hypercapnic metabolic alkalosis (hypochloremic alkalosis) may persist for a few days.

Rapidly developing hypercapnic acidosis is more disruptive to the patient's physiology and more likely to be life-threatening than slowly developing, chronic disease. Hypoxemia associated with hypoventilation is the major cause of morbidity in patients with acute respiratory acidosis.

There are numerous causes of hypoventilation leading to hypercapnic respiratory acidosis. Lack of central receptor sensitivity is a common cause in foals with neonatal encephalopathy. Central depression can also result from sedatives, head trauma, cerebral edema, or encephalitis. Neuromuscular disorders leading to hypoventilation include botulism, spinal cord injury, and tetanus. Respiratory fatigue can cause hypoventilation in weak neonates with low lung compliance. Restricted ventilation can result from fractured ribs, flail chest, pneumothorax, hemothorax, or diaphragmatic hernia. Upper airway obstruction leading to hypoventilation may result from nasal obstruction, pharyngeal disease (collapse, cysts), laryngeal disease (paresis, chondroids), laryngospasm, angioedema, tracheal collapse, or aspiration as well as other abnormalities. Lower airway obstruction can result from bronchospasm, bronchiolitis, pulmonary alveolar dysfunction, pneumonia, acute respiratory distress syndrome, or pulmonary edema. Hypercapnia can also result from a pulmonary perfusion defect such as may result from cardiac defects, cardiac arrhythmias, cardiac insufficiency, hypoperfusion, or shock.

Signs of mild to moderate hypercapnia include increased cardiac output, increased blood pressure, bounding pulse, and warm skin. These signs are the manifestations of a centrally mediated adrenergic surge as a response to hypercapnia. Clinical observations suggest that this response peaks with a P_aCO_2 of approximately 80 to 100 mmHg. Even in cases that are hypotensive, such as foals suffering from septic shock, there may be a transient improvement in perfusion as a result of this adrenergic stimulation. As the P_aCO_2 continues to rise the hypercapnia will result in direct organ depression (primarily cardiac and CNS) resulting in

decreased cardiac output (bradycardia and decreased myocardial contractility) and hypotension. Also systemic and cerebral vasodilation and pulmonary and renal vasoconstriction will occur. Other cardiac arrhythmias may also occur. Hypercapnic encephalopathy is primarily manifested by a transient increased central irritability followed by severe central depression, progressing to a non-responsive state and respiratory depression leading to respiratory arrest.

Therapy

When considering treatment of hypercapnia only the arterial pH should be considered. Hypercapnia should not be corrected if the arterial pH is alkalotic, normal, or mildly acidotic. With significant metabolic alkalosis, hypercapnia is appropriate. Current evidence suggests that mild hypercapnic acidosis (pH >7.2) may be beneficial in sepsis because of its anti-inflammatory effects (Curley et al., 2010; Ijland et al., 2010). It is unclear if this mild respiratory acidosis should be corrected.

The primary method of treating respiratory acidosis is increasing alveolar ventilation. Caffeine and doxapram have been used to increase ventilation when the cause of hypercapnic acidosis is depression of central receptors in foals. A small study of anesthetic-induced respiratory acidosis suggested that doxapram could be useful (Giguère et al., 2007). A retrospective study of the use of caffeine or doxapram in equine neonatal encephalopathy cases showed that doxapram therapy did not correct the acidosis despite decreasing the $P_a\text{CO}_2$. With caffeine therapy, the $P_a\text{CO}_2$ did not change yet the pH tended to normalize, but there was a concurrent confounding progressive metabolic alkalosis in the caffeine cases (Giguère et al., 2008). The mild respiratory acidosis these pharmacologic agents have been used to treat may be better left uncorrected. Definitive treatment for severe respiratory acidosis is mechanical ventilation, which has been described in foals (Palmer, 2005).

When hypoventilation is caused by upper airway obstruction, stenting the airway with an endotracheal tube to prevent collapse or placing a tracheostomy may resolve the problem. When hypoventilation is caused by lower airway obstruction, use of bronchodilators may resolve the problem.

Since hypercapnia will lead to hypoxemia when breathing room air, oxygen therapy is indicated. Careful monitoring of Cl and K concentrations, and supplementation as indicated, is important to support renal

compensation for the respiratory acidosis. Sodium bicarbonate therapy is contraindicated in the face of respiratory acidosis as it will add to the CO_2 load, thereby contributing to the acidosis.

Respiratory alkalosis

Respiratory alkalosis is marked by hypocapnia due to increased pulmonary excretion of CO_2 . Decreases in the HCO_3^- concentration (approximately 0.2 mEq/L for each mmHg decrease in P_{CO_2}) occurs within 5 to 10 minutes secondary to the equilibrium of HCO_3^- with CO_2 influenced by the law of mass action in the presence of carbonic anhydrase. Plasma $[\text{H}^+]$ decreases by approximately 0.75 nEq/L for every mmHg decrease in P_{CO_2} . The decrease in HCO_3^- should not be viewed as a decrease in buffer but rather the reflection of the transformation of a non-volatile acid (H^+) into a volatile acid (P_{CO_2}). Plasma potassium concentration decreases by approximately 0.2 mEq/L for every 0.1 increase in pH as a result of intracellular K/H exchange. Hypophosphatemia may develop and plasma chloride concentrations may increase.

There are several causes of hyperventilation. Hypoxemia stimulates hyperventilation when the $P_a\text{O}_2$ decreases below 60 mmHg. Central hyperventilation may occur in neonatal encephalopathy as a primary problem or secondary to hyperthermia. Hyperventilation can also be secondary to stimulation of pulmonary neuroreceptors in pneumonia, pneumothorax, hemothorax, acute respiratory distress syndrome, or interstitial lung disease. Hyperventilation may also occur secondary to pain, anxiety, fever, high adrenergic tone, meningoencephalitis, hepatic encephalopathy, or cerebral trauma. Hyperventilation may be seen in pregnancy, sepsis, liver failure, or heat exhaustion. Acute respiratory alkalosis can result in decreased cerebral blood flow because of local vasoconstriction, which may result in cerebral hypoxemia and neurologic abnormalities. This is self-limiting as the local increase in lactic acid secondary to tissue hypoxia results in vasodilation (Adrogué & Madias, 2011; Madias & Adrogué, 2009; Mehta & Emmett, 2009).

Therapy

Therapy is generally aimed at the underlying cause. In severe cases of central hyperventilation sedation with phenobarbital to depress the central receptors may be useful.

Mixed acid–base disorders

The term “mixed acid–base disorder” refers to a clinical condition in which two or more primary acid–base disorders coexist. They generally present with one obvious disturbance with what appears to be an inappropriate (excessive or inadequate) compensation. The “inappropriateness” of the compensatory process is the result of a separate primary disorder rather than the compensatory response itself. The expected degrees of compensation for primary acid–base disorders have been determined in humans by analysis of data from a large number of patients, and are expressed in the form of equations. When disorders influence the blood pH in opposite directions, the blood pH will be determined by the dominant disorder(s). If disorders cancel out each other’s effects, blood pH can be normal. When there is compensation for acid–base disorders, both $P_a\text{CO}_2$ and HCO_3^- are expected to change in the same direction (i.e., both are high or both are low). If $P_a\text{CO}_2$ and HCO_3^- have changed in opposite directions, the presence of a mixed acid–base disorder is expected. Compensation may be excessive, insufficient, or appropriate. One can also have an idea about the appropriateness of compensation from the degree of pH deviation.

Mixed acid–base disorders are common in critically ill patients and can lead to dangerous extremes of pH. Four or more independent abnormalities may be contributing to the final pH. Untangling these independent abnormalities can reveal the underlying pathophysiology that is placing the patient in jeopardy. When examining the information from a patient with a complex mixed acid–base disorder it is helpful to examine the four major influences on acid–base balance:

- 1 SID_A excluding lactate.
- 2 lactate plus other organic anions (UA);
- 3 abnormalities in the buffer base;
- 4 respiratory component.

Abnormalities of the SID_A (excluding lactate), whether brought about as appropriate renal compensation or produced as a primary abnormality, take time to develop and time to resolve, suggesting chronicity. As is apparent, abnormalities in the SID_A in these cases are a result primarily of the abnormality of $\text{Na} + \text{K}$ and Cl concentrations and are caused by renal (or placental) and/or gastrointestinal adjustments of these ions. Lactic acidosis and other organic anion acidoses are processes of abnormal intermediary metabolism, which can develop

rapidly and resolve rapidly. These abnormalities imply other underlying pathophysiologic forces at work. Abnormalities of the buffer base, which can have a large influence on the acid–base balance, with extreme levels of plasma proteins and phosphate are unusual; when present they reflect still different underlying pathophysiologies. And finally changes in respiratory acid excretion may reflect attempts at normal respiratory compensation or underlying neurorespiratory abnormalities. Examining each of these parts of the puzzle in turn will help the clinician to have a better understanding of why the pH value is normal or abnormal. It also points toward a better understanding of the underlying pathophysiology that is placing the patient at peril (DuBose, 2012).

In the complex disturbances of critically ill patients, alkalinizing and acidifying disturbances may both be present concurrently and may escape detection because of their offsetting effects. There are significant differences between the mechanisms causing acid–base imbalances. There are likewise significant differences in outcomes for patients developing acidosis from dilution, poisoning, hyperchloremia, excessive use of normal saline infusions, dysoxia, and other causes of increased lactate production. The acid–base abnormalities themselves may be of less clinical significance than previously thought.

Summary

This has been a short review of the underlying causes of metabolic acid–base disturbances and the strengths and weakness of the analytic tools designed to help understand the origin of the disturbance in clinical cases. Acute metabolic acidosis can be a complex problem and may be caused by an alteration in the SID or the buffer base. An altered SID reflects a change in the relative ratio of strong anions to strong cations. This change can be caused by anion gains as occur with lactic acidosis, renal acidosis, ketoacidosis, or hyperchloremia. Alternatively, cations may be lost, as occurs with severe diarrhea or renal tubular acidosis. Acute acidosis also may reflect increased free water relative to strong ions (dilutional acidosis), which may accompany excessive hypotonic fluid intake or the presence of excessive osmoles such as with hyperglycemia or alcohol poisoning (ethanol, methanol, isopropyl alcohol, ethylene

glycol). The plasma concentration of albumin and phosphate also can have an influence over acid–base balance by resulting in abnormal amounts of the buffer base, which in turn is reflected by the amount of the non-volatile weak acid present. The respiratory contribution to the acid–base balance is less complex but none the less important to consider. The techniques described in this chapter have been found useful for exploring acid–base disturbances in horses secondary to colic, diarrhea, and exercise (Navarro et al., 2005; Nappert & Johnson, 2001; Viu et al., 2010). They are equally useful in understanding acid–base abnormalities in neonatal foals as demonstrated by the examples in this chapter.

References

- Adrogué HJ, Madias NE. (2011) Respiratory acidosis, respiratory alkalosis, and mixed disorders. In: Floege J, Johnson RJ, Feehally J (eds) *Comprehensive Clinical Nephrology*, 4th edn. London: Mosby, pp. 176–92.
- Arroyo LG, Stampfli HR. (2007) Equine renal tubular disorders. *Vet Clin Equine* **23**:631–9.
- Astrup P, Jorgensen K, Siggaard-Andersen O. (1960) Acid-base metabolism: New approach. *Lancet* **i**:1035–9.
- Bagga A, Sinha A. (2007) Evaluation of renal tubular acidosis. *Indian J Pediatr* **74**:679–86.
- Boyd JH, Walley KR. (2008) Is there a role for sodium bicarbonate in treating lactic acidosis from shock? *Curr Opin Crit Care* **14**:379–83.
- Collings JL. (2010) Acid-base disorders. In: Marx JA, Hockberger RS, Walls RM, Adams JG, et al. (eds) *Marx–Rosen’s Emergency Medicine*, 7th edn. Philadelphia: Saunders Elsevier, pp. 1605–14.
- Constable PD. (1997) A simplified strong ion model for acid–base equilibria: Application to horse plasma. *J Appl Physiol* **83**:297–311.
- Corey HE. (2003) Stewart and beyond: New models of acid–base balance. *Kidney Int* **64**:777–87.
- Curley G, Contreras M, Nichol AD, Higgins BD, Laffey JG. (2010) Hypercapnia and acidosis in sepsis a double-edged sword? *Anesthesiology* **112**:462–72.
- DuBose TD. (2012) Disorders of acid–base balance. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM (eds) *Brenner & Rector’s The Kidney*, 9th edn. Philadelphia: Elsevier, pp. 595–631.
- Effros MR, Swenson ER. (2010) Acid–base balance. In: Mason CJ, Broaddus VC, Martin TR, et al. (eds) *Murray and Nadel’s Textbook of Respiratory Medicine*, 5th edn. Philadelphia: Saunders Elsevier, pp. 134–58.
- Emmett M, Narins RG. (1977) Clinical use of the anion gap. *Medicine* **56**:38–54.
- Fencel V, Leith DE. (1993) Stewart’s quantitative acid–base chemistry: Applications in biology and medicine. *Resp Physiol* **91**:1–16.
- Figge J, Mydosh T, Fencel V. (1992) Serum proteins and acid–base equilibria: a follow-up. *J Lab Clin Med* **120**:713–19.
- Firmin CJ, Kruger TE, Davids R. (2007) Proximal renal tubular acidosis in pregnancy. *Gynecol Obstet Invest* **63**:39–44.
- Giguère S, Sanchez LC, Shih A, Szabo NJ, Womble AY, Robertson SA. (2007) Comparison of the effects of caffeine and doxapram on respiratory and cardiovascular function in foals with induced respiratory acidosis. *Am J Vet Res* **68**:1407–16.
- Giguère S, Slade JK, Sanchez LC. (2008) Retrospective comparison of caffeine and doxapram for the treatment of hypercapnia in foals with hypoxic-ischemic encephalopathy. *J Vet Intern Med* **22**:401–5.
- Gilfix BM, Bique M, Magder S. (1993) A physical chemical approach to the analysis of acid–base balance in the clinical setting. *J Crit Care* **8**:187–97.
- Guidet B, Soni N, Della Rocca G, et al. (2010) A balanced view of balanced solutions. *Critical Care* **14**:325–37.
- Gunnerson KJ, Saul M, He S, Kellum JA. (2006) Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Crit Care* **10**:R22.
- Greenbaum LA. (2011) Electrolyte and acid–base disorders. In: Kliegman RM, Stanton BF, Geme III JW, Schor NF, Behman RE (eds) *Nelson Textbook of Pediatrics*, 19th edn. Philadelphia: Saunders Elsevier, pp. 212–42.
- Hasselbalch KA. (1916) The calculation of blood pH via the partition of carbon dioxide in plasma and oxygen binding of the blood as a function of plasma pH. *Biochem Z* **78**:112–44.
- Hemstreet BA. (2004) Antimicrobial-associated renal tubular acidosis. *Ann Pharmacother* **38**:1031–8.
- Henderson LJ. (1907) The theory of neutrality regulation in the animal organism. *Am J Physiol* **18**:427–48.
- Ijland MM, Heunks LM, van der Hoeven JG. (2010) Bench-to-bedside review: Hypercapnic acidosis in lung injury – from ‘permissive’ to ‘therapeutic.’ *Crit Care* **14**:237–47.
- Jorgensen K, Astrup P. (1957) Standard bicarbonate, its clinical significance, and a new method for its determination. *Scand J Clin Lab Invest* **9**:122–32.
- Kellum JA. (2005) Determinants of plasma acid–base balance. *Crit Care Clin* **21**:329–46.
- Kellum JA. (2007a) Acid–base disorders and strong ion gap. *Contrib Nephrol* **156**:158–66.
- Kellum JA. (2007b) Disorders of acid–base balance. *Crit Care Med* **35**:2630–6.
- Kellum JA, Song M, Li J. (2004) Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol* **286**:R686–R692.
- Kurtz I, Kraut J, Ornekian V, Nguyen MK. (2008) Acid–base analysis: a critique of the Stewart and bicarbonate-centered approaches. *Am J Physiol Renal Physiol* **294**:F1009–F1031.

- Latta TA. (1832) Relative to the treatment of cholera by the copious injection of aqueous and saline fluids into the veins. *Lancet* **ii**:274–7.
- Madias NE, Adrogué HJ. (2009) Respiratory acidosis and alkalosis. In: Greenberg A (ed.) *Primer on Kidney Diseases*, 5th edn. Philadelphia: Saunders, pp. 91–7.
- Mehta AN, Emmett M. (2009) Approach to acid-base disorders. In: Greenberg A (ed.) *Primer on Kidney Diseases*, 5th edn. Philadelphia: Saunders, pp. 98–107.
- Morgan TJ, Cowley DM, Weier SL, Venkatesh B. (2007) Stability of the strong ion gap versus the anion gap over extremes of PCO₂ and pH. *Anaesth Intensive Care* **35**:370–3.
- Nappert G, Johnson PJ. (2001) Determination of the acid-base status in 50 horses admitted with colic between December 1998 and May 1999. *Can Vet J* **42**:703–7.
- Navarro M, Monreal L, Segura D, Armengou L, Añor S. (2005) A comparison of traditional and quantitative analysis of acid-base and electrolyte imbalances in horses with gastrointestinal disorders. *J Vet Intern Med* **19**:871–7.
- O’Shaughnessy WB. (1831) Proposal of a new method of treating the blue epidemic cholera by the injection of highly-oxygenised salts into the venous system. *Lancet* **i**:366–71.
- Palmer JE. (2005) Ventilatory support of the critically ill foal. *Vet Clin North Am: Equine Pract* **21**:457–86.
- Rachoin JS, Weisberg LS, McFadden CB. (2010) Treatment of lactic acidosis: appropriate confusion. *J Hosp Med* **5**:E1–E7; doi: 10.1002/jhm.600.
- Rastegar A. (2009) Clinical utility of Stewart’s method in diagnosis and management of acid-base disorders. *Clin J Am Soc Nephrol* **4**:1267–74.
- Ring T, Frische S, Nielsen S. (2005) Clinical review: Renal tubular acidosis – a physicochemical approach. *Crit Care* **9**: 573–80.
- Rocher LL, Tannen RL. (1986) The clinical spectrum of renal tubular acidosis. *Ann Rev Med* **37**:319–31.
- Shannon M. (2007) Acid-base, fluid, and electrolyte balance. In: Shannon M (ed.) *Haddad and Winchester’s Clinical Management of Poisoning and Drug Overdose*, 4th edn. Philadelphia: Saunders Elsevier, pp. 105–18.
- Siggaard-Andersen O. (1963) Blood acid-base alignment nomogram. Scales for pH, PCO₂, base excess of whole blood of different hemoglobin concentrations. Plasma bicarbonate and plasma total CO₂. *Scand J Clin Lab Invest* **15**:211–17.
- Siggaard-Andersen O. (1977) The Van Slyke equation. *Scand J Clin Lab Invest* **37**(Suppl. 146):15–20.
- Singer RB, Hastings AB. (1948) Improved clinical method for estimation of disturbances of acid-base balance of human blood. *Medicine (Baltimore)* **27**:223–42.
- Stewart PA. (1981) How to Understand Acid Base Balance. *A Quantitative Acid–Base Primer for Biology and Medicine*. New York: Elsevier.
- Van Slyke DD. (1921) Studies of acidosis: XVII. *The normal and abnormal variations in the acid base balance of the blood*. *J Biol Chem* **48**:153–76.
- Van Slyke DD. (1928) Sendroy: Studies of gas and electrolyte equilibria in blood: XV. Line charts for graphic calculations by Henderson–Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. *J Biol Chem* **79**:781–98.
- Vernon C, LeTourneau JL. (2010) Lactic acidosis: recognition, kinetics, and associated prognosis. *Crit Care Clin* **26**:255–83.
- Viu J, Jose-Cunilleras E, Armengou L, et al. (2010) Acid-base imbalances during a 120km endurance race compared by traditional and simplified strong ion difference methods. *Equine Vet J* **42**(Suppl. 38):76–82.
- Wang Y, Xu T. (2011) Acidosis, acid-sensing ion channels, and neuronal cell death. *Mol Neurobiol* **44**:350–8.
- Wooten EW. (2003) Calculation of physiological acid-base parameters in multicompartments systems with application to human blood. *J Appl Physiol* **95**:2333–44.